

Transition metal-free synthesis of 3-trifluoromethyl chromones via tandem C-H trifluoromethylation and chromone annulation of enaminones

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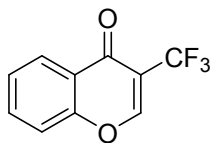
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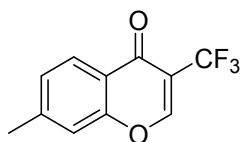
General experimental information

All experiments were carried out under air atmosphere. The enaminones were synthesized following literature process.¹ Other chemicals and solvents used in the experiments were obtained from commercial sources and used directly without further treatment. The ¹H and ¹³C NMR spectra were recorded in 400 MHz apparatus in CDCl₃ solvent. The frequencies for ¹H NMR and ¹³C NMR test are 400 MHz and 100 MHz, respectively. The chemical shifts were reported in ppm with TMS as internal standard. Melting points were tested in X-4A instrument without correcting temperature, and the HRMS data for all new products were obtained under ESI model in a mass spectrometer equipped with TOF analyser.

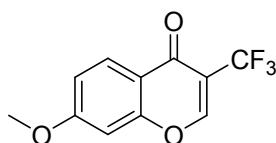
Characterization data of all products



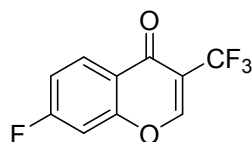
3-(Trifluoromethyl)-4H-chromen-4-one (3a).² Yield 72%, 31 mg; light yellow solid; mp 92-93 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1 H), 8.27 (d, *J* = 7.8 Hz, 1 H), 7.76 (t, *J* = 7.8 Hz, 1 H), 7.56-7.47 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.8, 156.0, 155.8 (q, *J* = 7 Hz), 134.8, 126.3 (d, *J* = 32 Hz), 124.3, 122.2 (d, *J* = 270 Hz), 118.3, 116.0 (d, *J* = 31 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F).



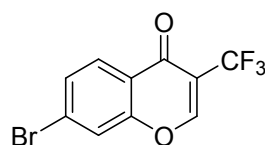
7-Methyl-3-(trifluoromethyl)-4H-chromen-4-one (3b). Yield 70%, 32 mg; light yellow solid; mp 121-122 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.26 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 2.51 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 156.1, 155.6 (q, *J* = 7 Hz), 146.5, 126.8 (d, *J* = 208 Hz), 123.6, 122.0, 120.9, 118.0, 115.8 (d, *J* = 30 Hz), 21.80; ¹⁹F NMR (376 MHz, CDCl₃): δ -64.4 (s, 3 F); ESI-HRMS Calcd for C₁₁H₈F₃O₂ [M+H]⁺ 229.0471, found 229.0478.



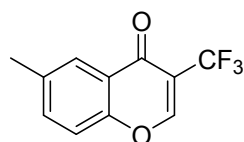
7-Methoxy-3-(trifluoromethyl)-4H-chromen-4-one (3c).² Yield 68%, 33 mg; light yellow solid; mp 118-119 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.31-8.22 (m, 1 H), 8.21-7.99 (m, 1 H), 7.10-6.99 (m, 1 H), 6.98-6.82 (m, 1 H), 3.92 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 164.9, 157.8, 155.4 (q, *J* = 7 Hz), 127.4, 118.0, 115.5, 100.6, 56.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -64.4 (s, 3 F).



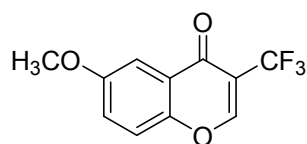
7-Fluoro-3-(trifluoromethyl)-4H-chromen-4-one (3d).² Yield 69%, 32 mg; white solid; mp 60-61 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.33-8.25 (m, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 171.7, 166.1 (d, *J* = 256 Hz), 157.0 (d, *J* = 13 Hz), 155.5 (q, *J* = 7 Hz), 128.78 (d, *J* = 11 Hz), 126.0, 123.3, 120.9 (d, *J* = 50 Hz), 117.9, 116.2 (d, *J* = 30 Hz), 115.3 (d, *J* = 23 Hz), 105.2 (d, *J* = 26 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F), -100.3 (s, 1 F).



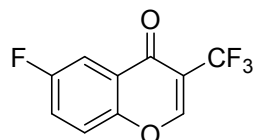
7-Bromo-3-(trifluoromethyl)-4H-chromen-4-one (3e). Yield 65%, 38 mg; light yellow solid; mp 135-136 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (s, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.74-7.70 (m, 1 H), 7.63-7.59 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 156.0, 155.8 (d, *J* = 7 Hz), 129.3, 128.8 (d, *J* = 266 Hz), 123.2 (d, *J* = 11 Hz), 121.5, 120.6; ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F); ESI-HRMS Calcd for C₁₀H₅BrF₃O₂ [M+H]⁺ 292.9420, found 292.9426.



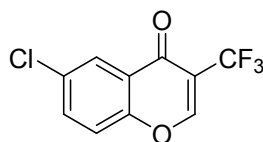
6-Methyl-3-(trifluoromethyl)-4H-chromen-4-one (3f).² Yield 75%, 34 mg; white solid; mp 125-126 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.31-8.27 (m, 1 H), 8.04-7.99 (m, 1 H), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 2.47 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.8, 155.6 (q, *J* = 7 Hz), 154.3, 136.7, 136.0, 125.4, 123.9, 123.6, 120.9, 118.0, 115.7 (q, *J* = 30 Hz), 20.9; ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F).



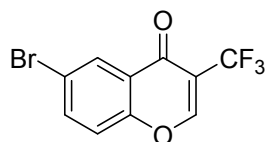
6-Methoxy-3-(trifluoromethyl)-4H-chromen-4-one (3g).² Yield 61%, 30 mg; white solid; mp 101-102 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, *J* = 1.2 Hz, 1 H), 7.61 (d, *J* = 3.0 Hz, 1 H), 7.45 (d, *J* = 9.2 Hz, 1H), 7.32 (dd, *J* = 9.2, 3.0 Hz, 1 H), 3.91 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 157.8, 155.4 (q, *J* = 7 Hz), 150.8, 125.1, 124.7, 123.7, 121.0, 119.7, 115.2 (q, *J* = 31 Hz), 105.3, 77.3, 56.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -64.4 (s, 3 F).



6-Fluoro-3-(trifluoromethyl)-4H-chromen-4-one (3h).² Yield 65%, 30 mg; white solid; mp 87-88 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.34 (s, 1 H), 7.88 (dd, *J* = 7.8, 2.8 Hz, 1 H), 7.57 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.52-7.46 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 180.0 (d, ⁴*J*_{C-F} = 2 Hz), 161.4, 158.9, 155.9 (q, *J* = 7 Hz), 152.2 (d, ⁴*J*_{C-F} = 2 Hz), 125.6 (d, ³*J*_{C-F} = 7 Hz), 123.4, 123.1 (d, ²*J*_{C-F} = 25 Hz), 120.7, 120.6 (d, ³*J*_{C-F} = 8 Hz), 115.4 (d, ²*J*_{C-F} = 30 Hz), 111.2 (d, ²*J*_{C-F} = 24 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F), -112.7 (s, 1 F).

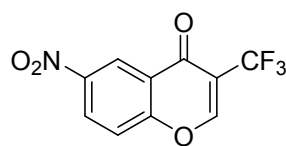


6-Chloro-3-(trifluoromethyl)-4H-chromen-4-one (3i).² Yield 67%, 33 mg; light yellow solid; mp 143-144 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1 H), 8.22-8.16 (m, 1 H), 7.73-7.66 (m, 1 H), 7.53-7.47 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 171.6, 155.9 (q, *J* = 7 Hz), 154.3, 135.1, 132.7, 125.5, 125.2, 123.3, 120.6, 120.1, 116.0 (d, *J* = 32 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ -64.5 (s, 3 F).

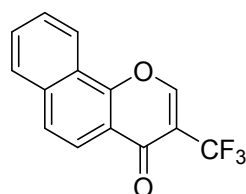


6-Bromo-3-(trifluoromethyl)-4H-chromen-4-one (3j).² Yield 62%, 36 mg; light yellow solid; mp 107-108 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 7.72 (s, 1 H), 7.63-7.59 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ

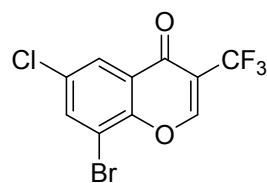
172.0, 156.0, 155.8 (q, $J = 7$ Hz), 133.3, 130.2, 129.3, 127.5, 126.0, 123.3, 123.2, 121.5, 120.6, 116.4 (q, $J = 30$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ -64.5 (s, 3 F).



6-Nitro-3-(trifluoromethyl)-4H-chromen-4-one (3k). Yield 35%, 18 mg; light yellow solid; mp 105-106 °C; ^1H NMR (400 MHz, CDCl_3): δ 9.11 (d, $J = 2.6$ Hz, 1 H), 8.60 (dd, $J = 8.0, 2.6$ Hz, 1 H), 8.41-8.38 (m, 1 H), 7.74 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.2, 158.6, 156.2 (q, $J = 7$ Hz), 145.6, 129.2, 124.5, 122.9, 122.7, 120.3, 120.2, 116.8 (d, $J = 31$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ -64.6 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{10}\text{H}_5\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 260.0165, found 260.0160.

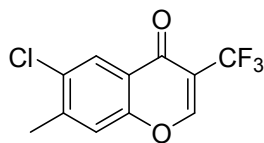


3-(Trifluoromethyl)-4H-benzo[h]chromen-4-one (3l). Yield 70%, 37 mg; light yellow solid; mp 168-169 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.51-8.44 (m, 2 H), 8.16 (d, $J = 8.0$ Hz, 1 H), 7.97-7.94 (m, 1 H), 7.83 (d, $J = 8.0$ Hz, 1 H), 7.78-7.70 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 154.9 (q, $J = 7$ Hz), 153.7, 136.2, 130.0, 128.3, 127.8, 126.6, 123.6, 123.5, 122.1, 120.9, 120.9, 120.3, 118.2, 117.2 (q, $J = 30$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ -64.6 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{14}\text{H}_8\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 265.0471, found 265.0477.

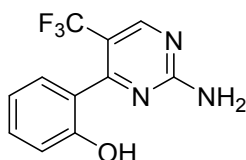


8-Bromo-6-chloro-3-(trifluoromethyl)-4H-chromen-4-one (3m). Yield 58%, 38 mg; light yellow solid; mp 72-73 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.41-8.39 (m, 1 H), 8.16 (d, $J = 2.4$ Hz, 1 H), 7.95 (d, $J = 2.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.0, 155.9 (q, $J = 7$ Hz), 151.4, 138.0, 132.9, 126.0, 124.9, 123.0, 120.3, 116.3 (d, J

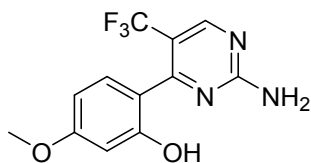
= 31 Hz), 113.0; ^{19}F NMR (376 MHz, CDCl_3): δ -64.7 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{10}\text{H}_4\text{BrClF}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 326.9030, found 326.9036.



6-chloro-7-methyl-3-(trifluoromethyl)-4H-chromen-4-one (3n). Yield 71%, 37 mg; white solid; mp 140-141 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.28 (s, 1 H), 8.16 (s, 1 H), 7.41 (s, 1 H), 2.52 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.5, 155.8 (q, J = 7 Hz), 154.2, 144.5, 133.3, 125.6, 123.3 (d, J = 20 Hz), 120.7, 120.1, 115.8 (d, J = 30 Hz), 20.8; ^{19}F NMR (376 MHz, CDCl_3): δ -64.5 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{11}\text{H}_7\text{ClF}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 263.0081, found 263.0085.

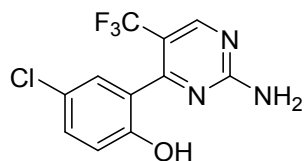


2-(2-Amino-5-(trifluoromethyl)pyrimidin-4-yl)phenol (5a). Yield 59%, 30 mg; light yellow solid; mp 200-201 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.59 (s, 1 H), 8.55 (s, 1 H), 7.44 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.07 (d, J = 7.2 Hz, 1 H), 6.90-6.80 (m, 2 H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 165.7, 164.7, 157.0 (q, J = 5 Hz), 154.7, 130.4, 129.3, 126.4, 125.4, 123.7, 118.6, 115.8, 112.0 (q, J = 31 Hz), 79.4 (t, J = 33 Hz); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -56.9 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 256.0692, found 256.0699.

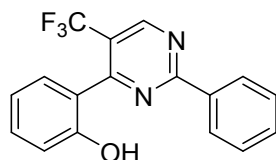


2-(2-Amino-5-(trifluoromethyl)pyrimidin-4-yl)-5-methoxyphenol (5b). Yield 65%, 37 mg; yellow solid; mp 212-213 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.84 (s, 1 H), 8.54 (s, 1 H), 7.43 (s, 2 H), 7.04 (d, J = 8.0 Hz, 1 H), 6.44 (d, J = 7.0 Hz, 2 H), 3.74 (s, 3 H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 165.4, 164.5, 161.3, 157.3 (q, J = 4 Hz), 156.4, 130.3, 129.2, 125.1 (d, J = 268 Hz), 117.9, 111.9 (q, J = 30 Hz), 104.6, 101.5,

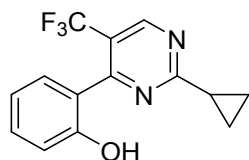
55.4; ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$): δ -56.5 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 286.0798, found 286.0808.



2-(2-Amino-5-(trifluoromethyl)pyrimidin-4-yl)-4-chlorophenol (5c). Yield 55%, 32 mg; yellow solid; mp 91-92 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.96 (s, 1 H), 8.59 (s, 1 H), 7.52 (s, 2 H), 7.30 (dd, J = 8.0, 2.6 Hz, 1H), 7.16 (d, J = 2.6 Hz, 1 H), 6.91 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 164.7, 164.0, 157.2 (q, J = 4 Hz), 153.8, 130.2, 128.8, 127.0, 126.3, 123.6, 122.2, 117.5, 111.8 (q, J = 31 Hz); ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$): δ -57.0 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{11}\text{H}_8\text{ClF}_3\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 290.0303, found 290.0310.



2-(2-Phenyl-5-(trifluoromethyl)pyrimidin-4-yl)phenol (5d). Yield 40%, 25 mg; light yellow solid; mp 118-119 °C; ^1H NMR (400 MHz, CDCl_3): δ 9.20 (s, 1 H), 8.46-8.41 (m, 2 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.60-7.52 (m, 3 H), 7.48-7.43 (m, 1 H), 7.15-7.10 (m, 1 H), 7.04-6.99 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.0, 163.9, 158.6 (q, J = 6 Hz), 157.5, 135.2, 133.6, 132.5, 130.5 (q, J = 5 Hz), 129.1, 128.9, 124.7, 122.0, 119.9, 119.4, 119.2, 119.0, 118.3; ^{19}F NMR (376 MHz, CDCl_3): δ -56.6 (s, 3 F); ESI-HRMS Calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 317.0896, found 317.0901.



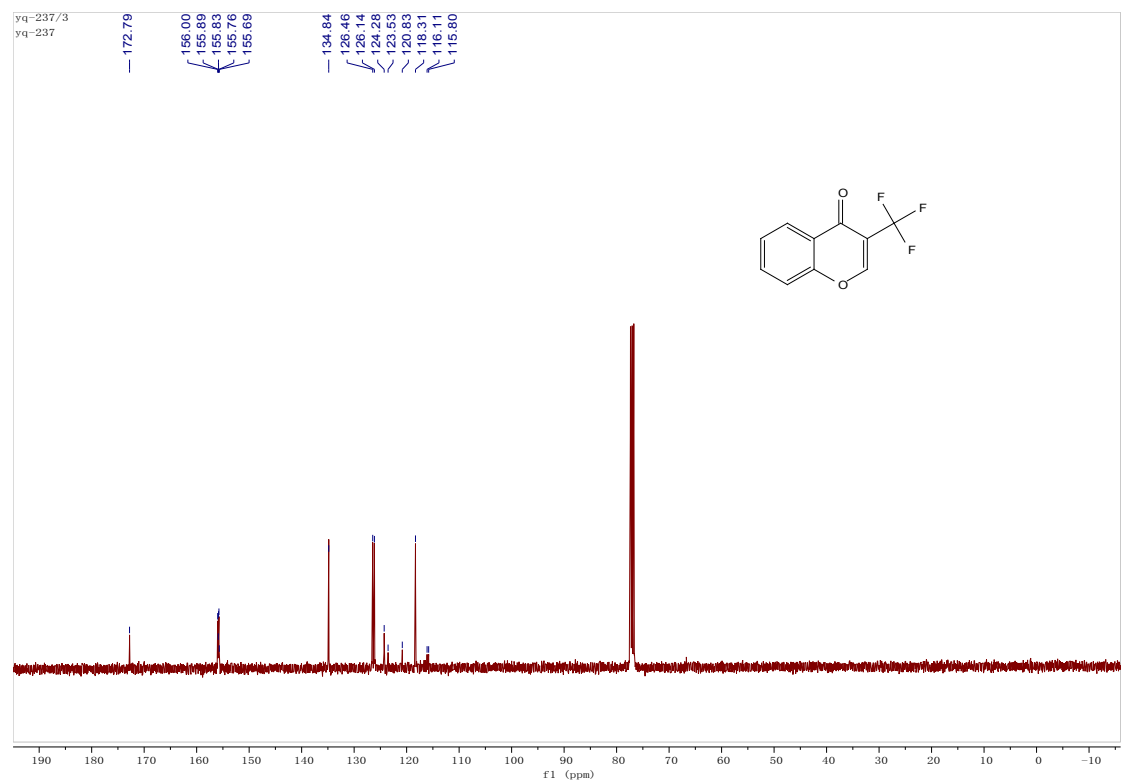
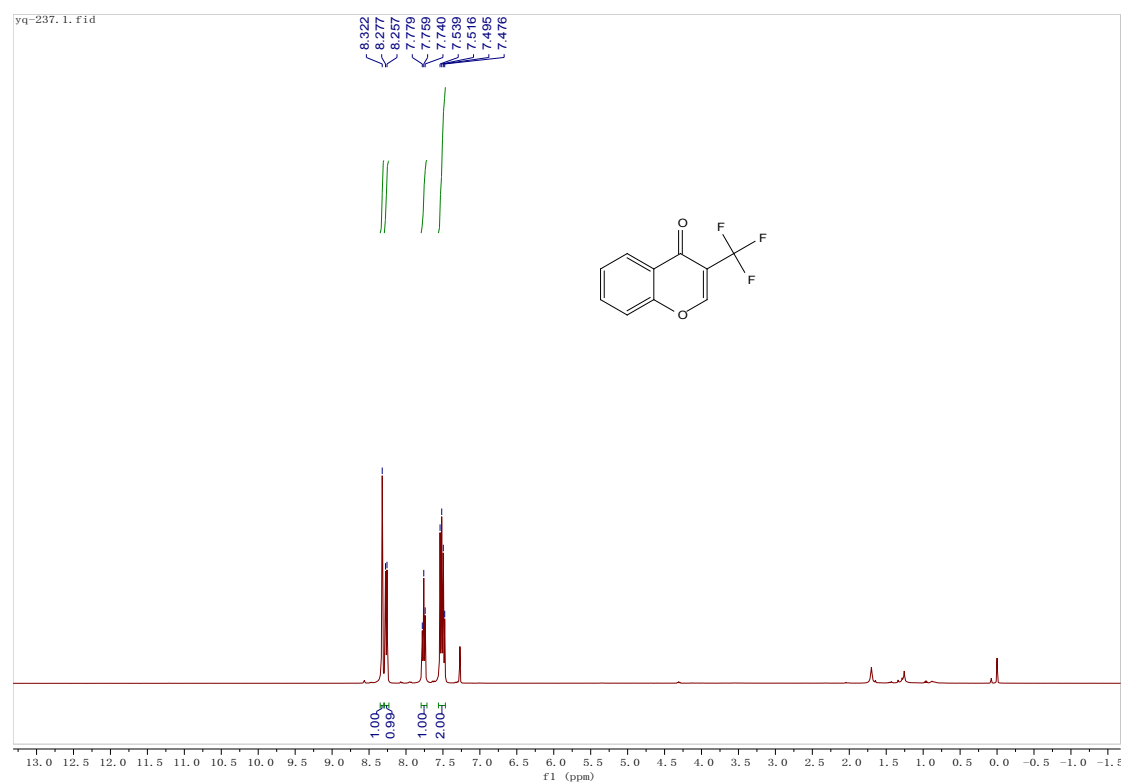
2-(2-Cyclopropyl-5-(trifluoromethyl)pyrimidin-4-yl)phenol (5e). Yield 52%, 29 mg; yellow solid; mp 90-91 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.95 (s, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.43-7.38 (m, 1 H), 7.09-7.04 (m, 1 H), 6.99-6.93 (m, 1 H), 2.39-2.32 (m, 1 H), 1.28-1.23 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.5, 163.3, 157.9 (q, J = 6 Hz), 157.7, 133.4, 130.5, 130.5, 130.4, 130.4, 124.8, 122.1, 119.7,

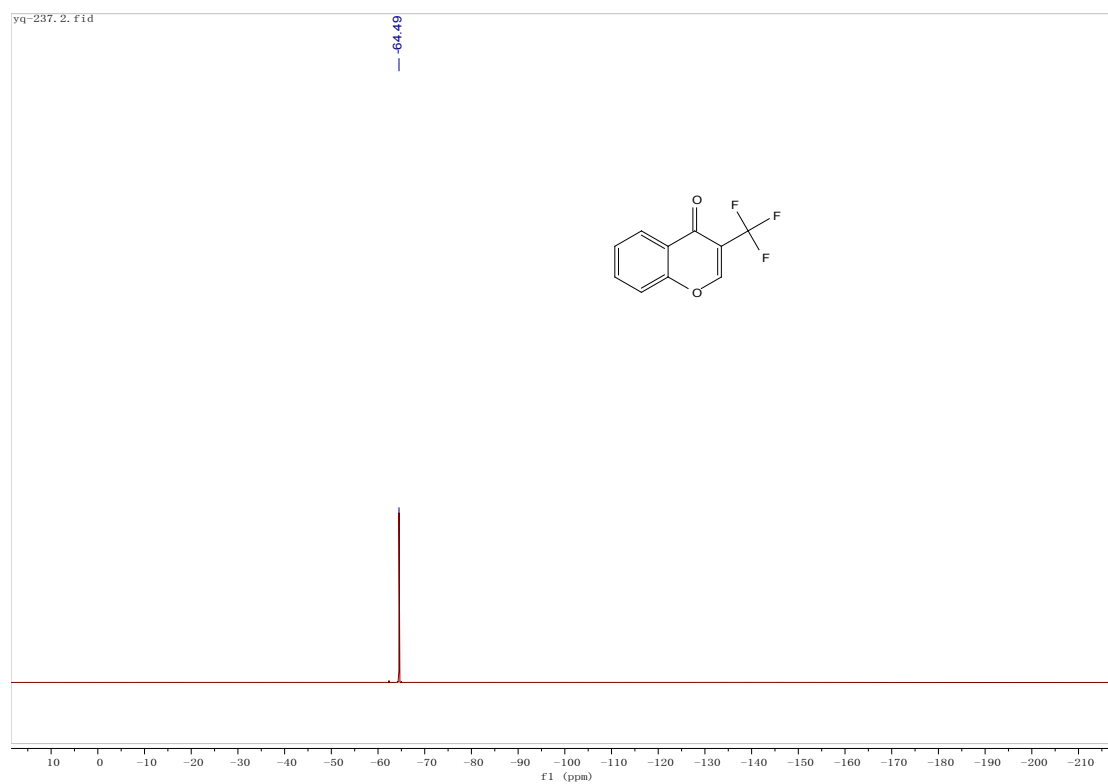
118.9, 118.2, 18.5, 12.3; ^{19}F NMR (376 MHz, CDCl_3): δ -56.5 (s, 3 F); ESI-HRMS
Calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 281.0896, found 281.0901.

Reference

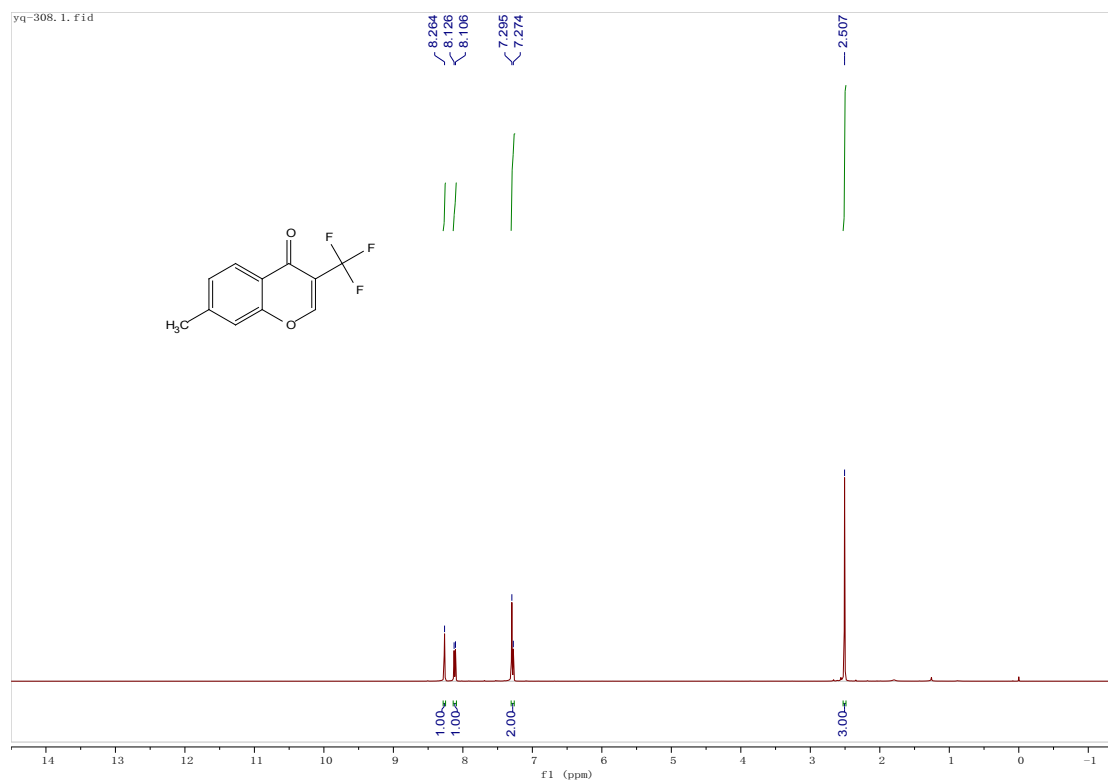
1. K. S. Levchenko, I. S. Semenova, V. N. Yarovenko, P. S. Shmelin and M. M. Krayushkin, *Tetrahedron Lett.* 2012, **53**, 3630.
2. H. Xiang, Q. Zhao, Z. Tang, J. Xiao, P. Xia, C. Wang, C. Yang, X. Chen and H. Yang, *Org. Lett.* 2017, **19**, 146-149.

¹H, ¹³C and ¹⁹F NMR spectra of all products

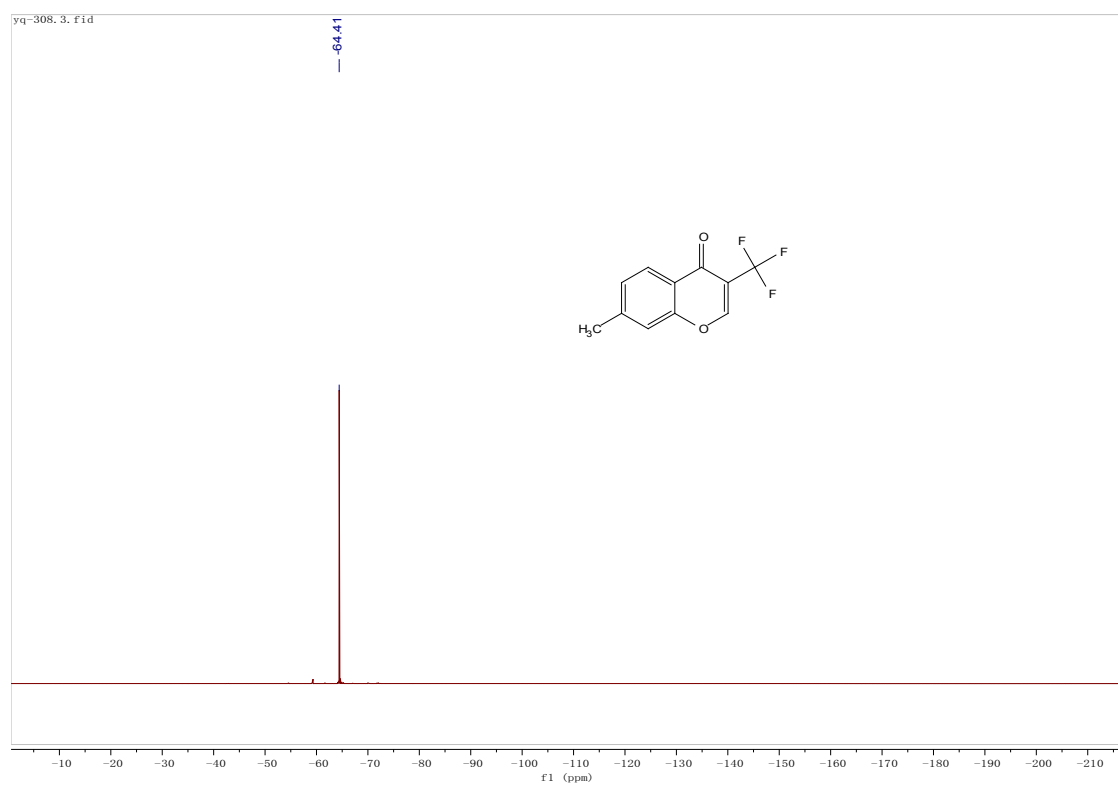
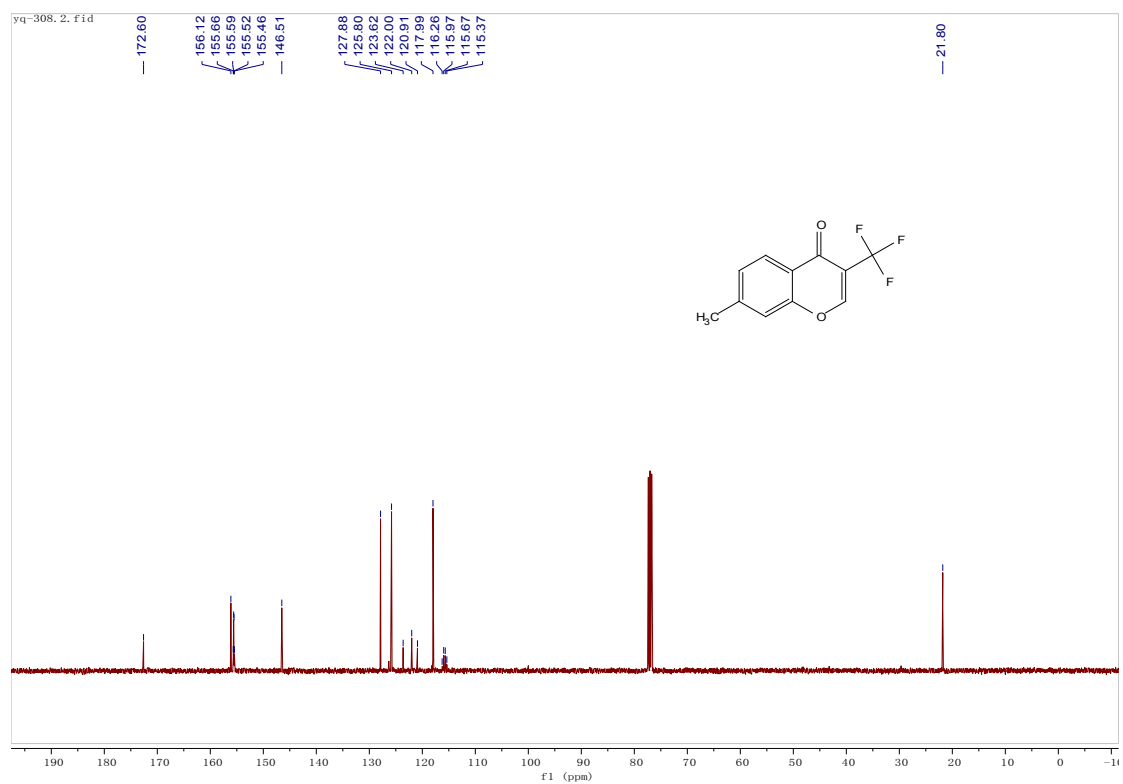




3a

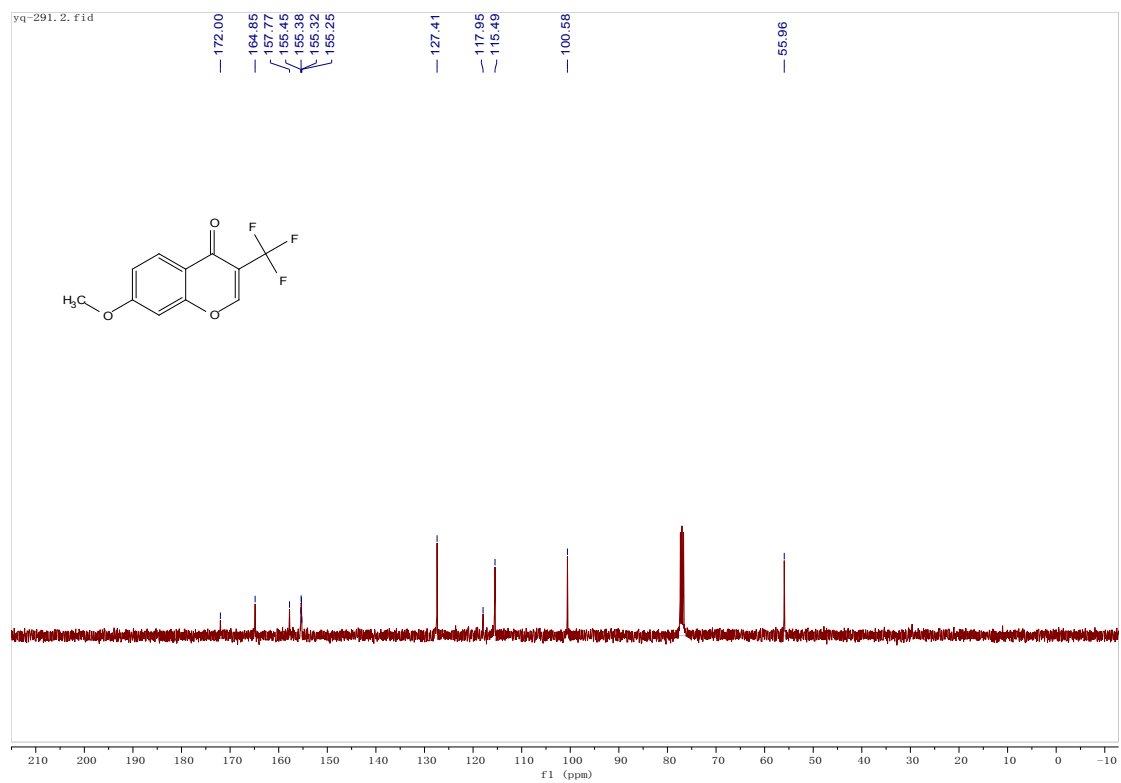
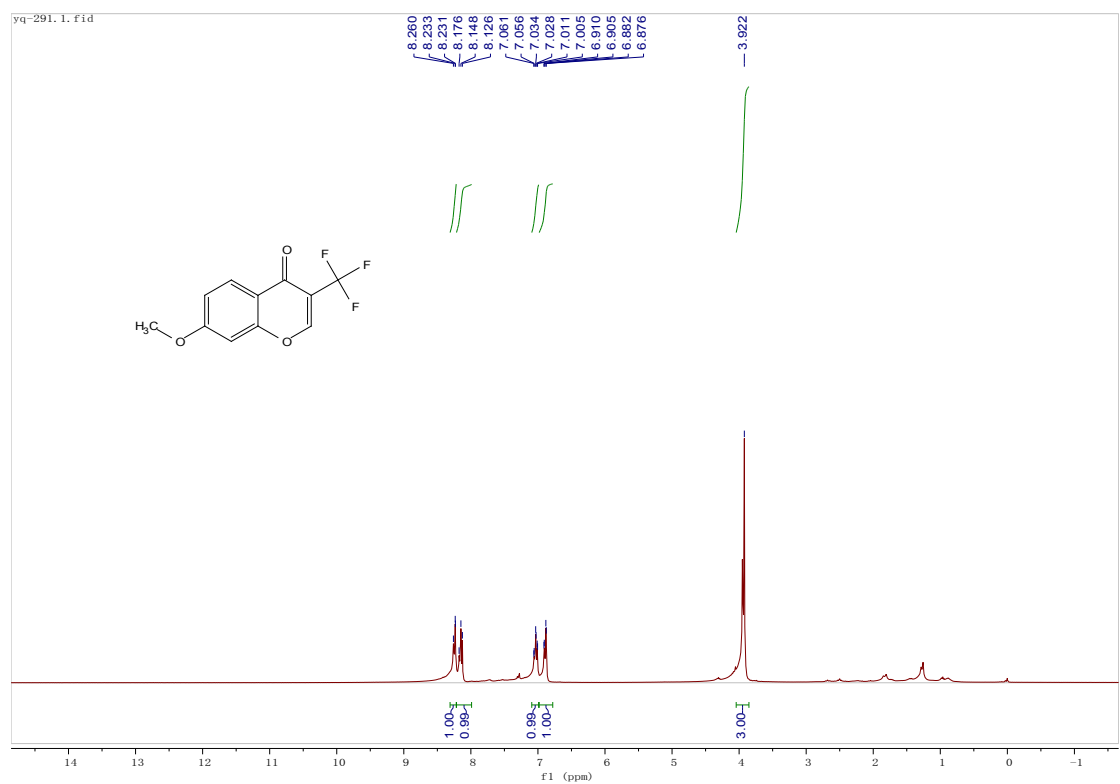


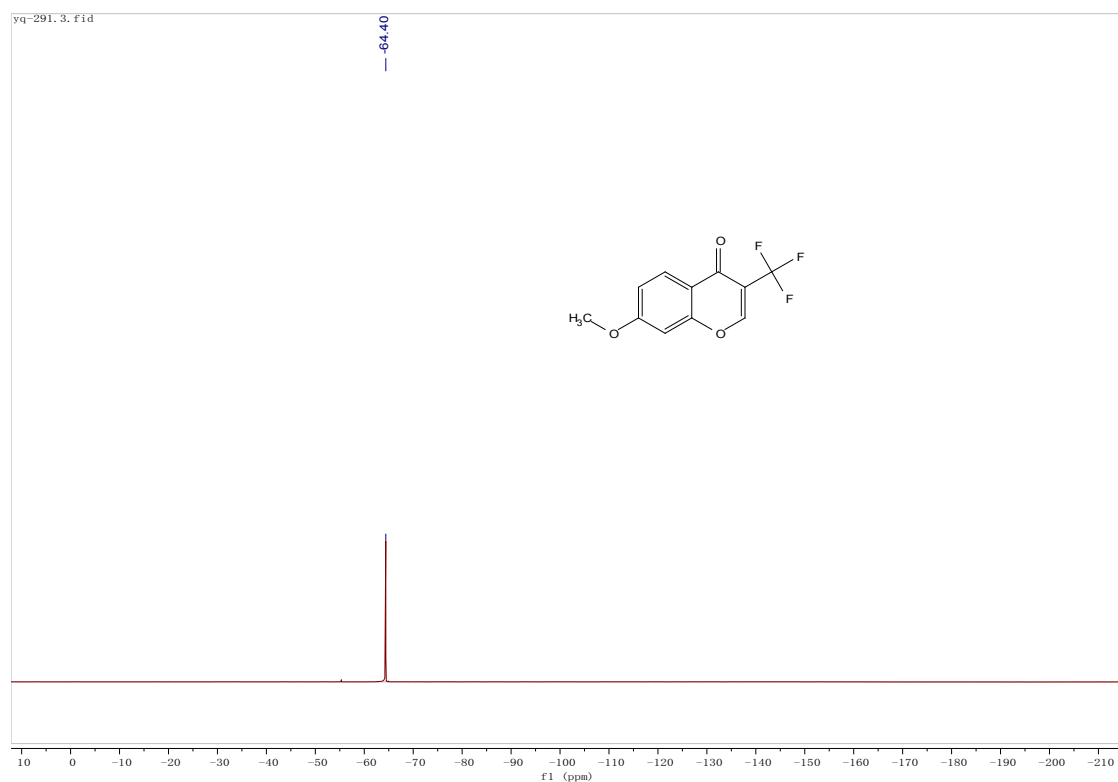
S10



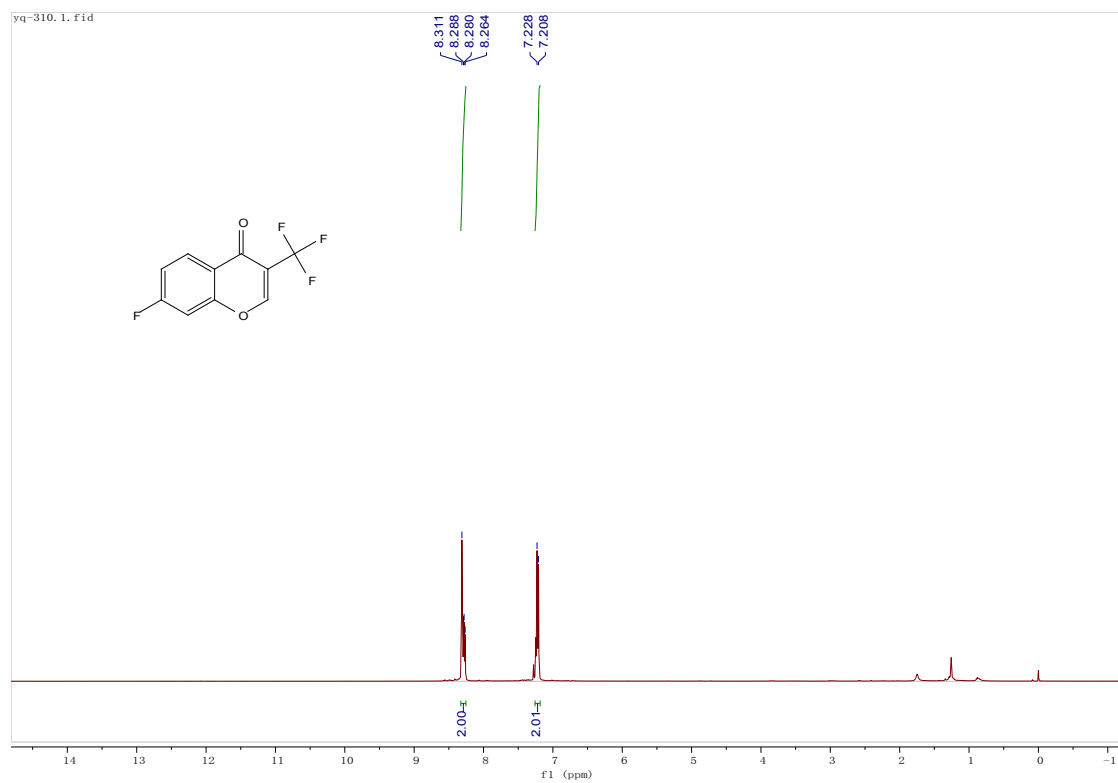
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S11

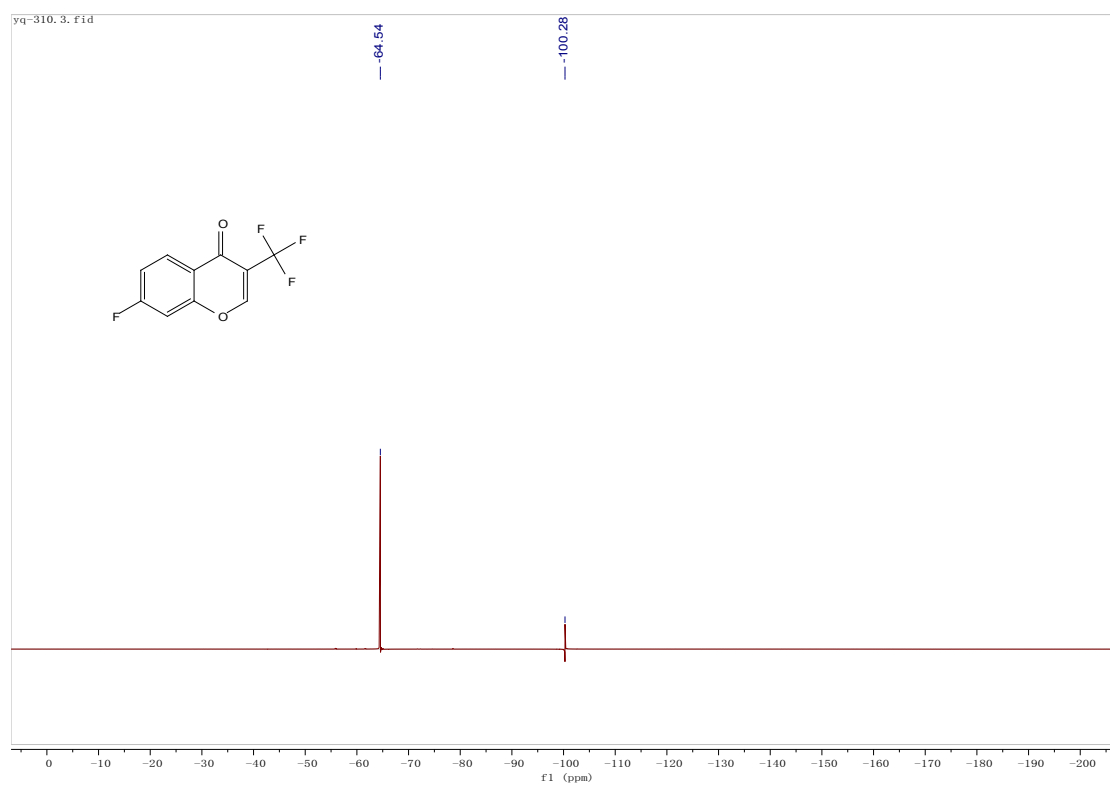
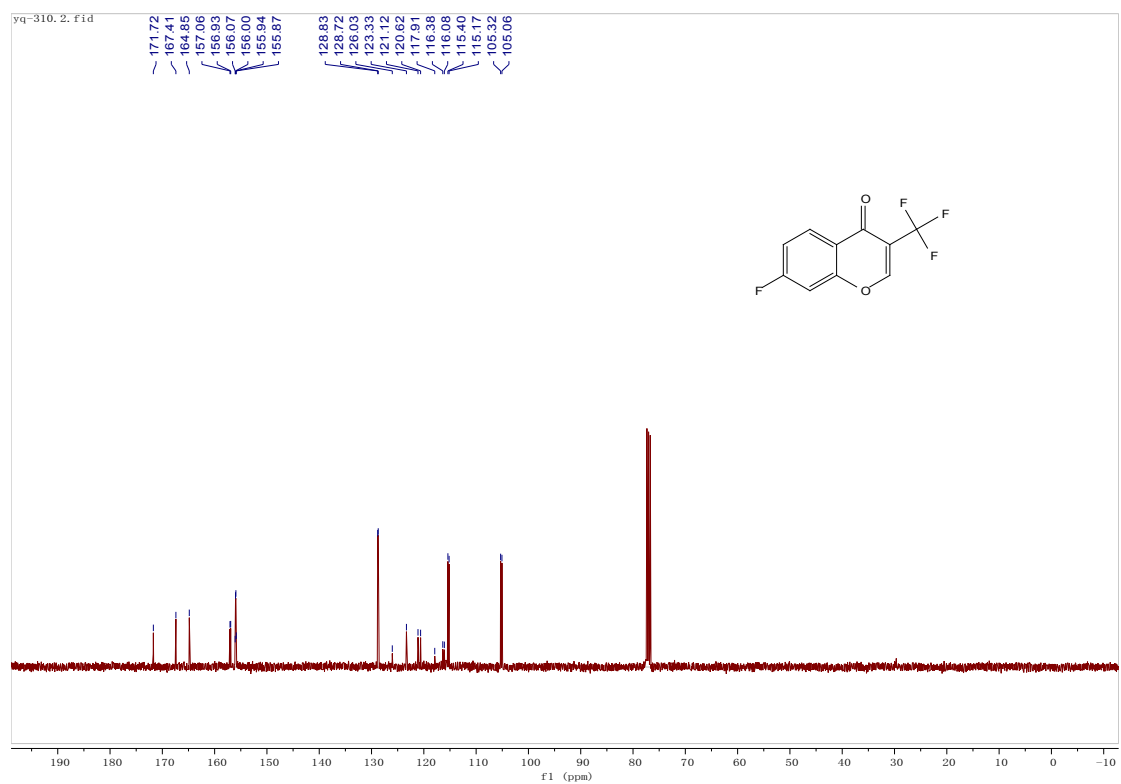




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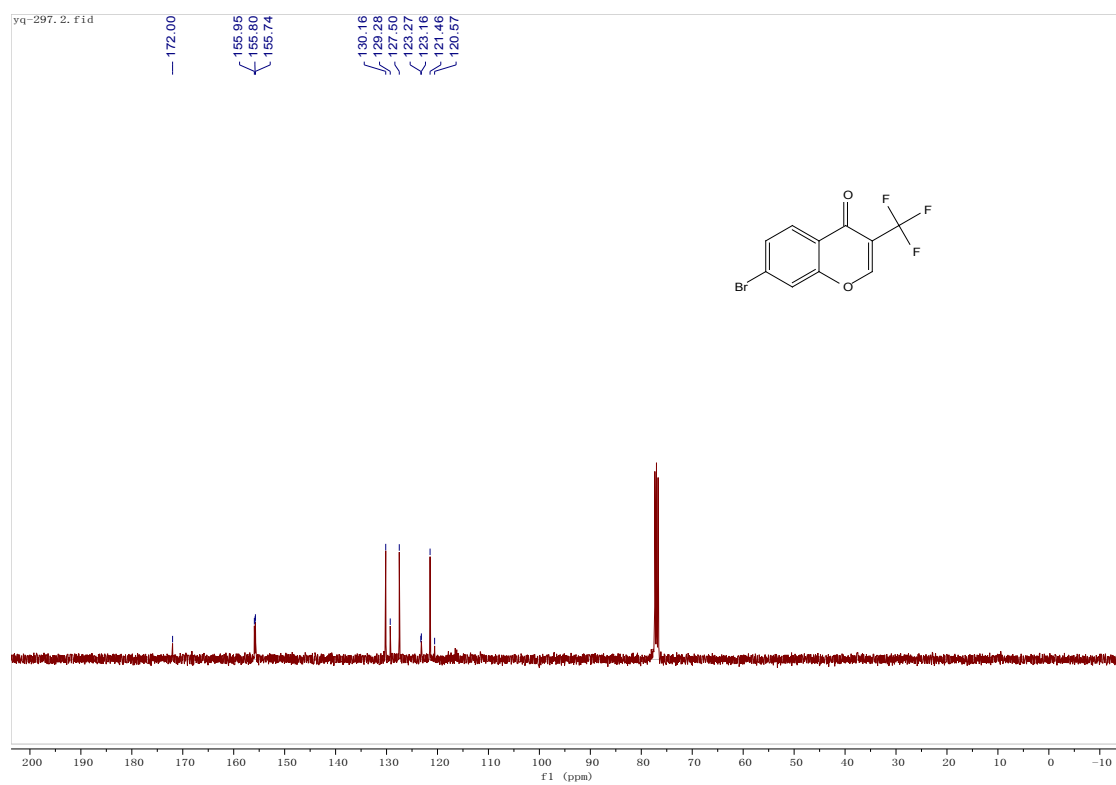
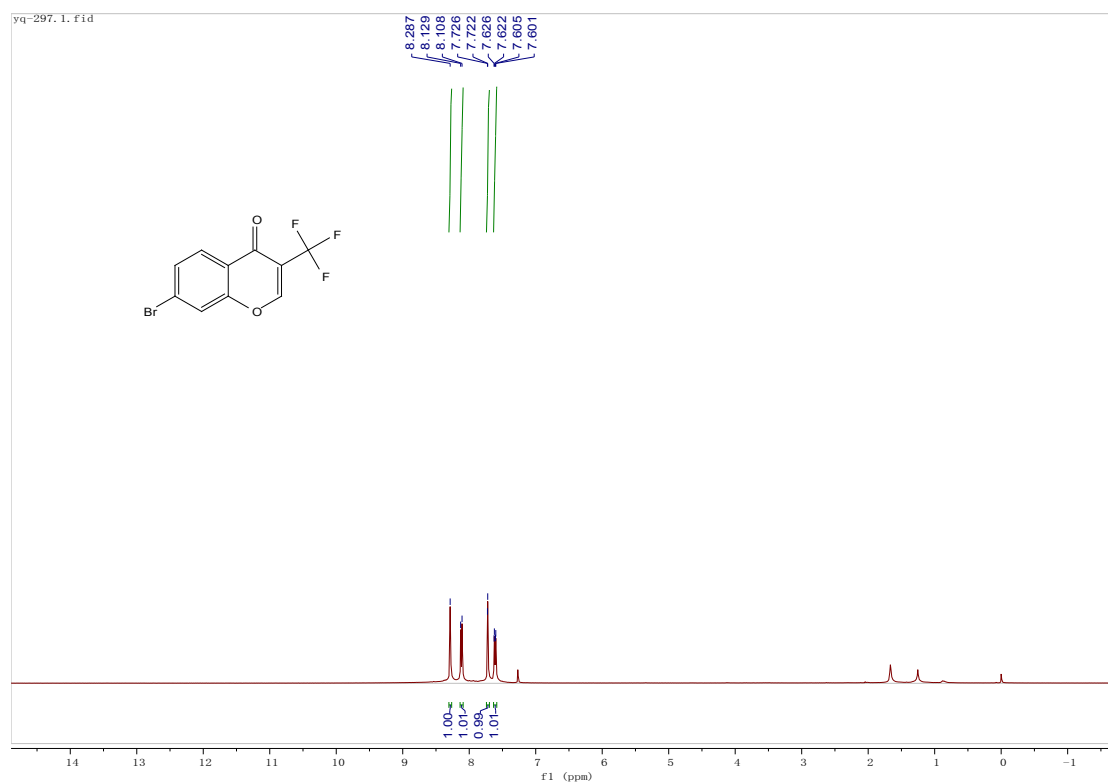


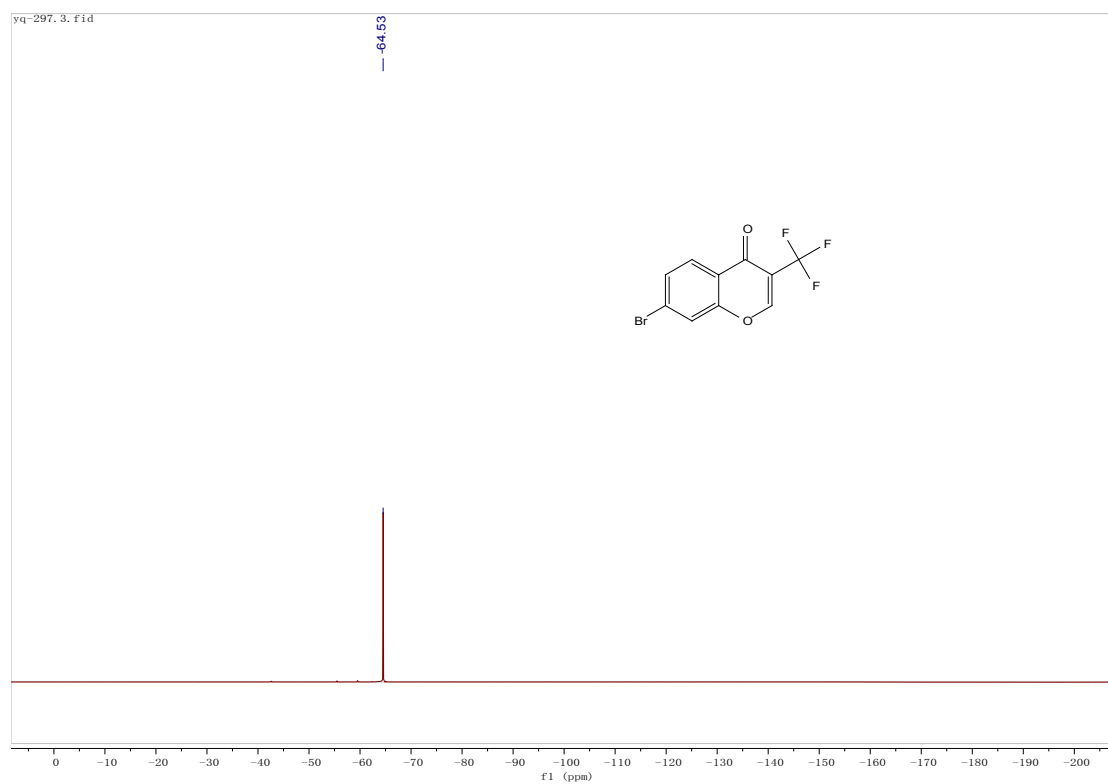
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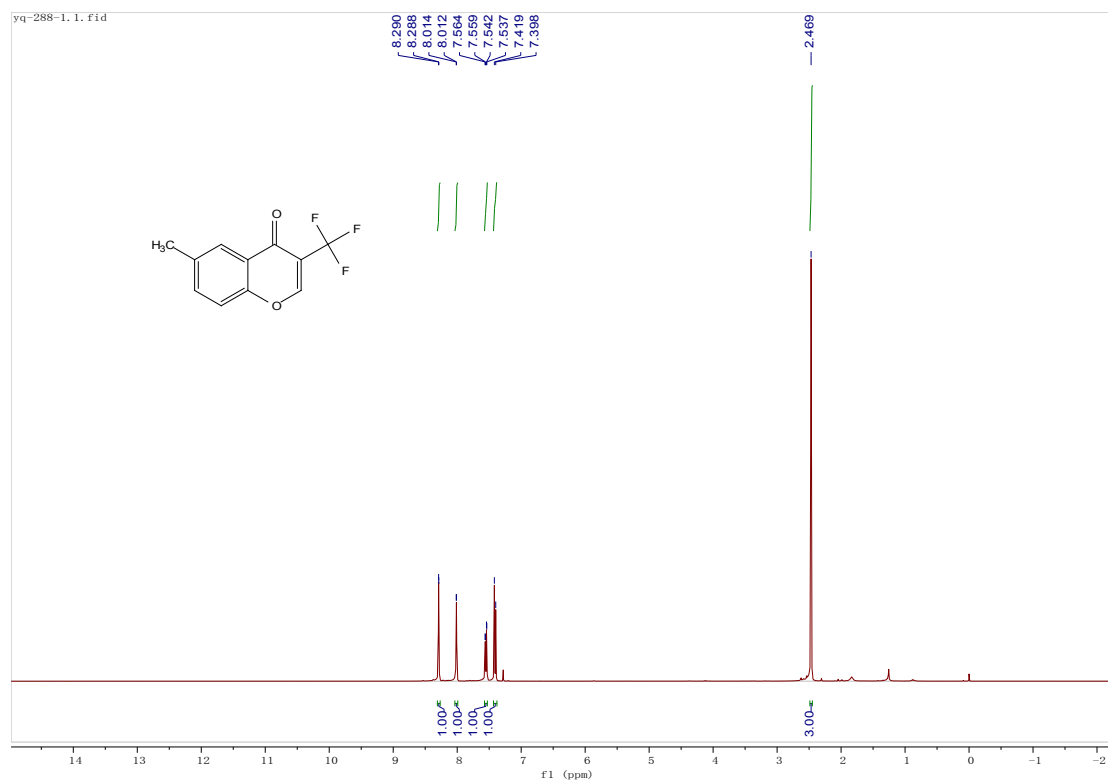
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S14

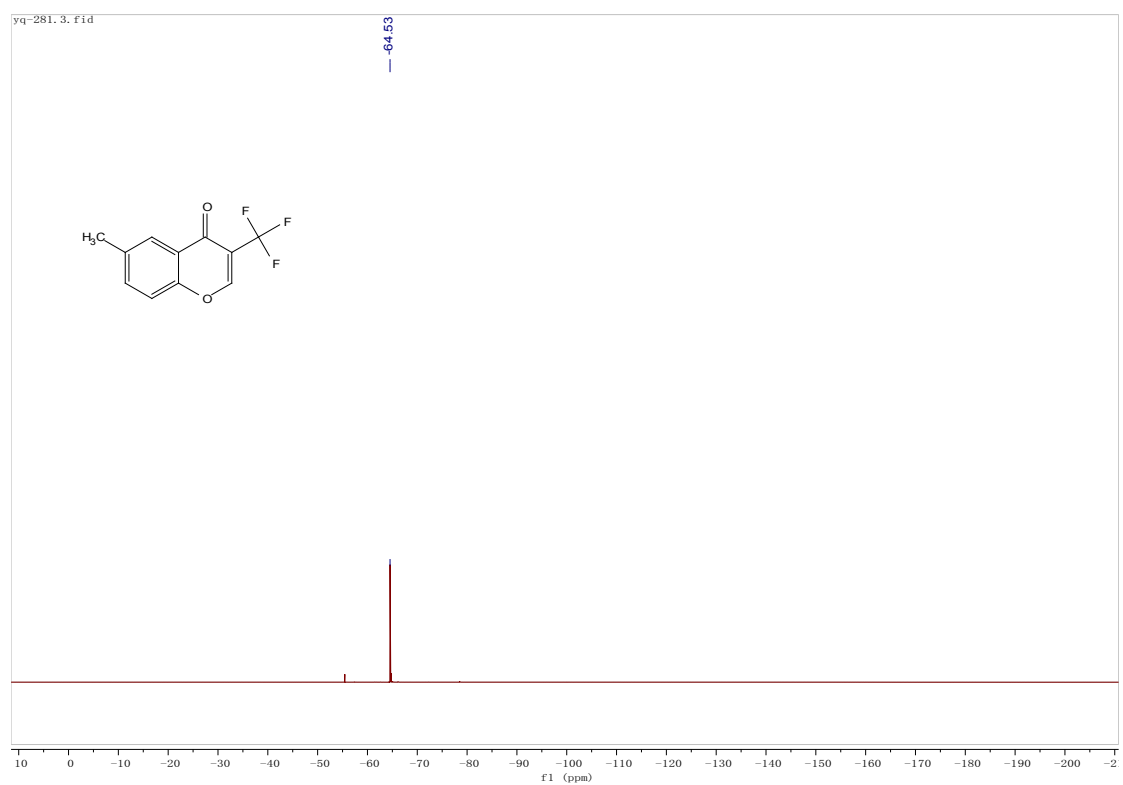
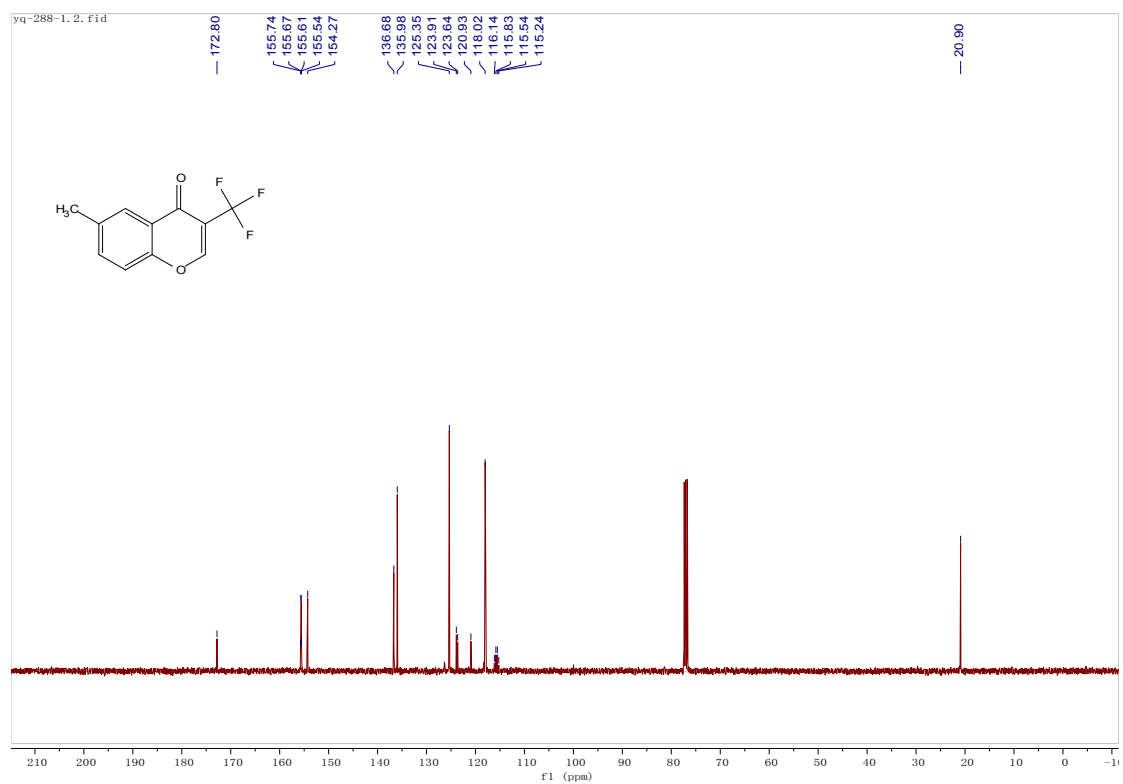




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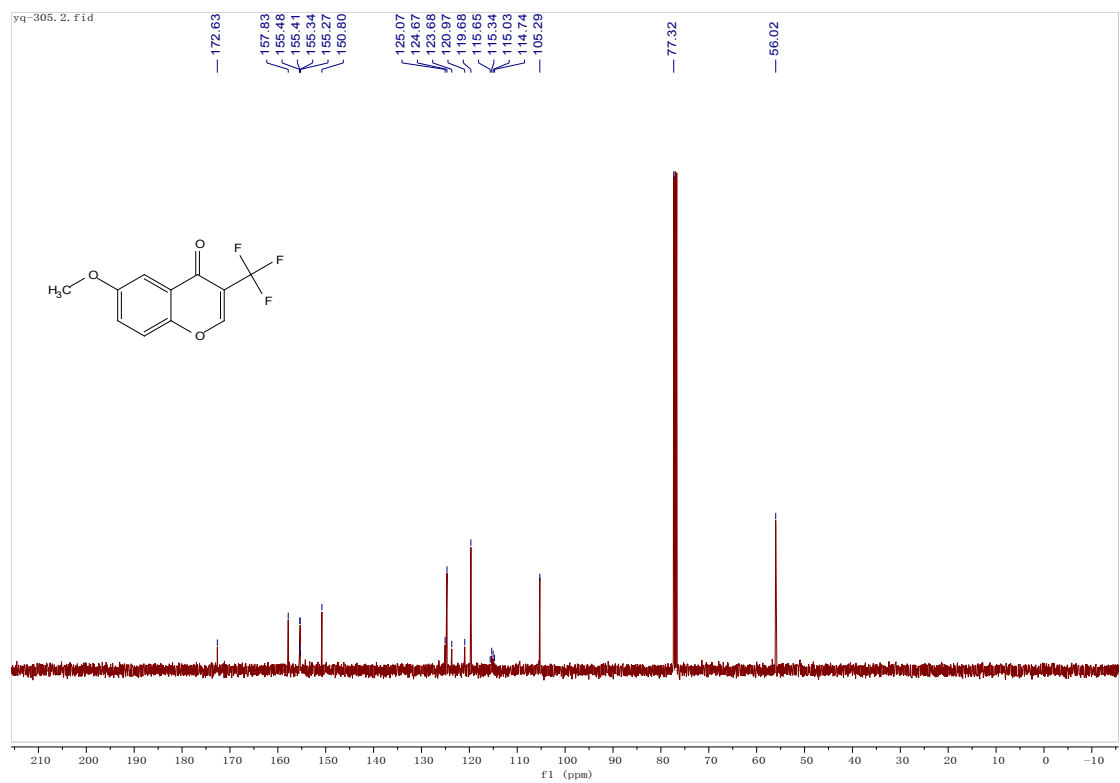
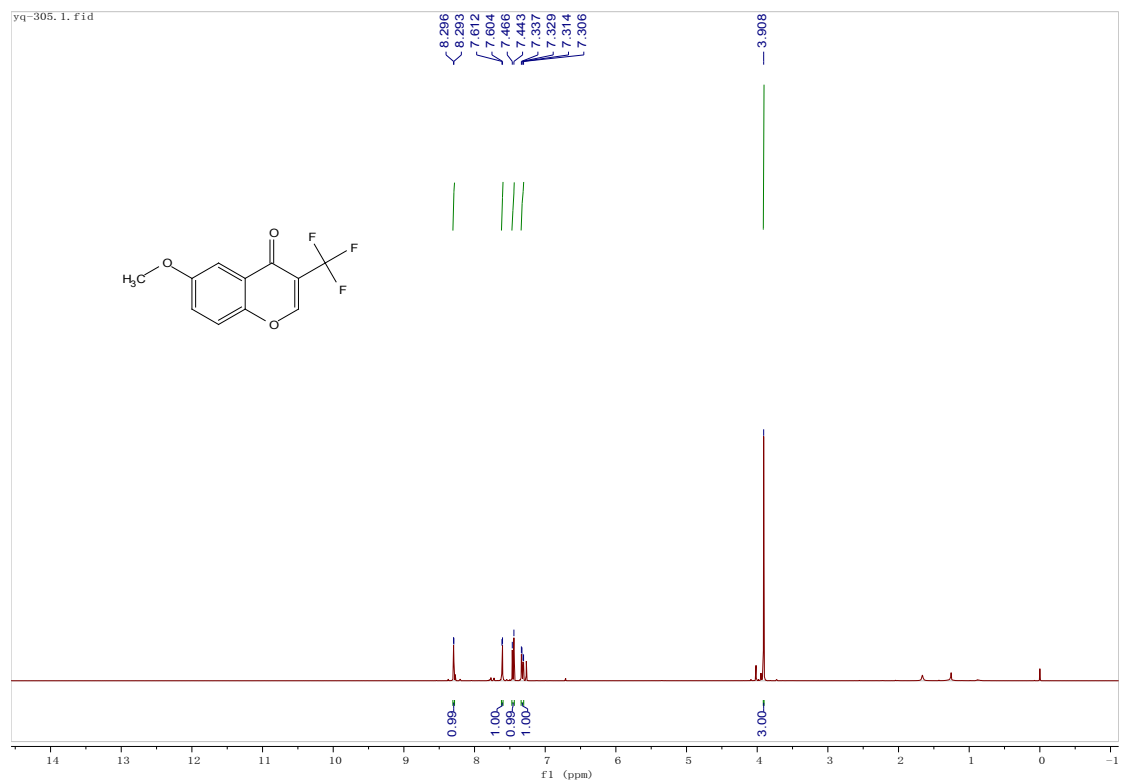


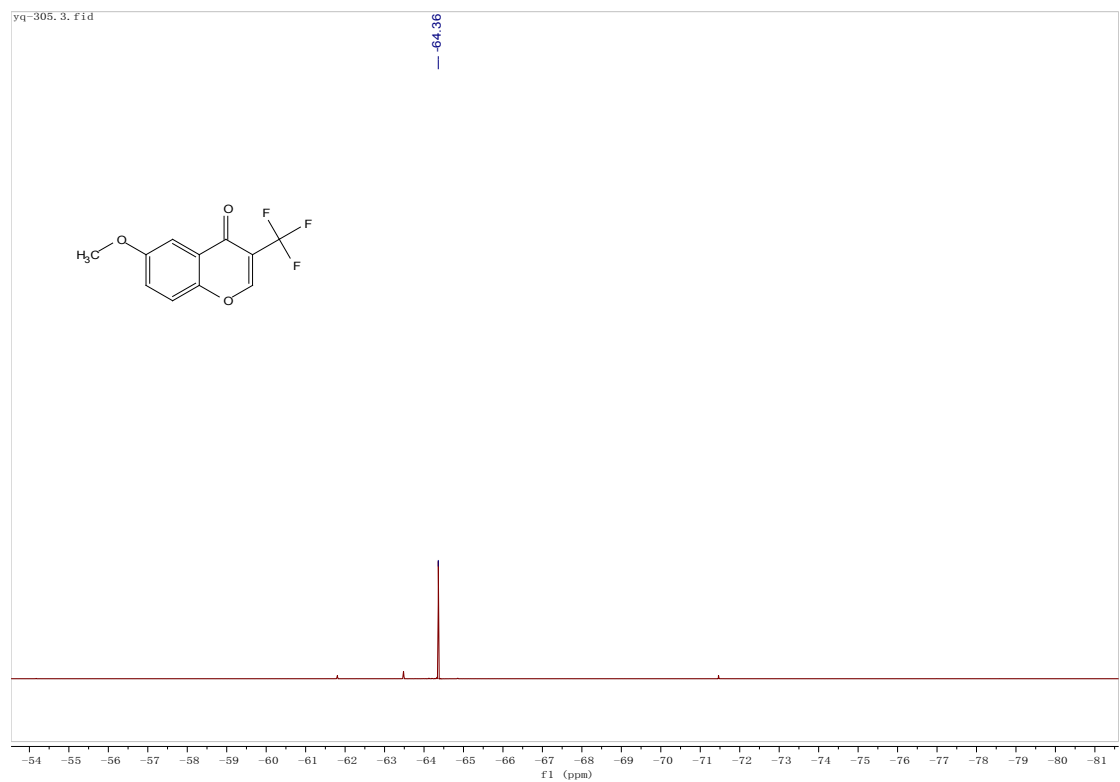
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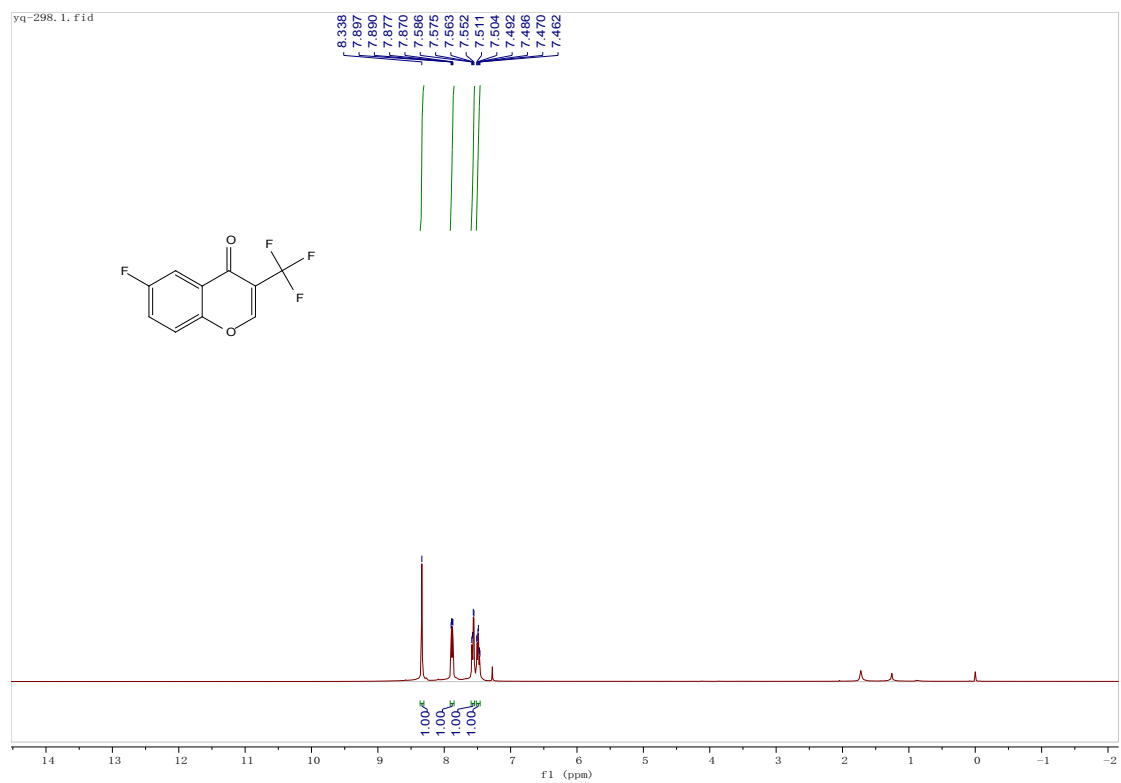
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S17

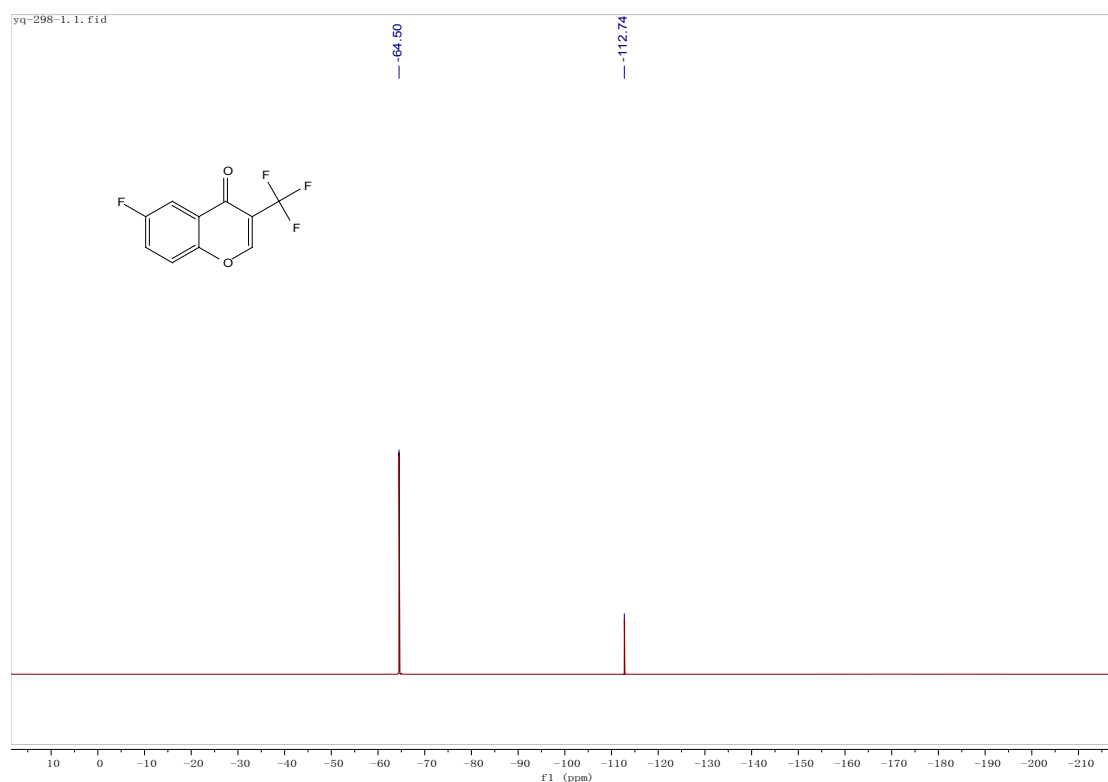
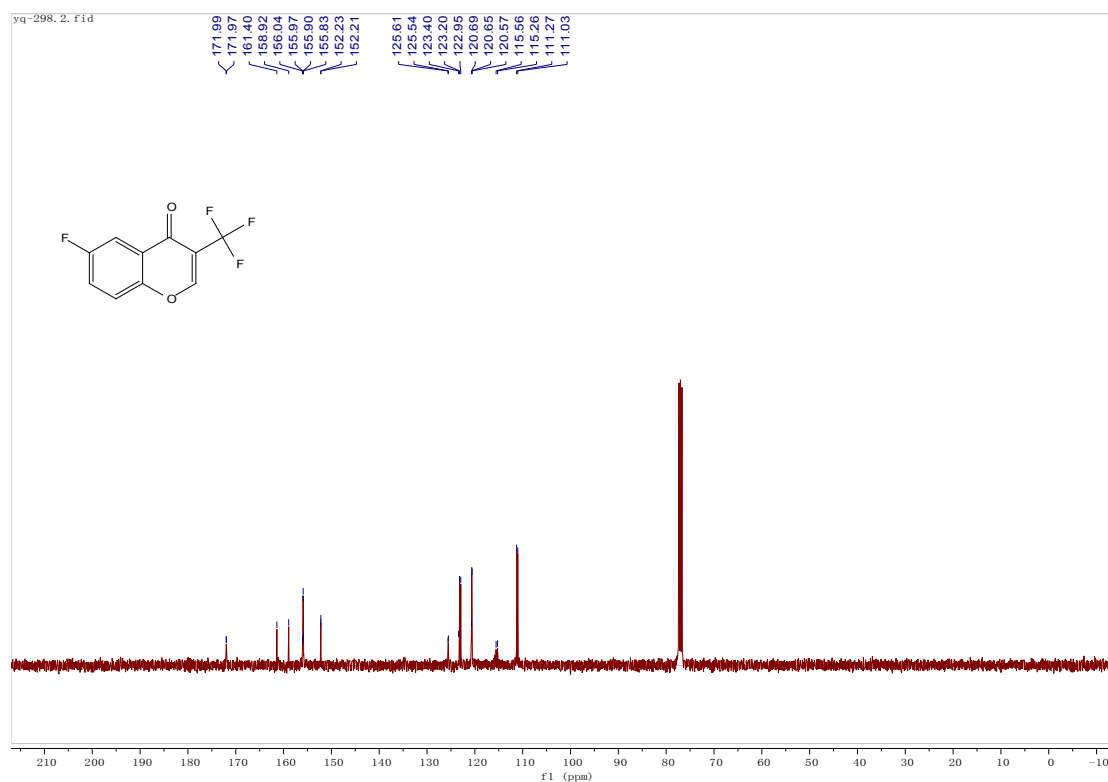




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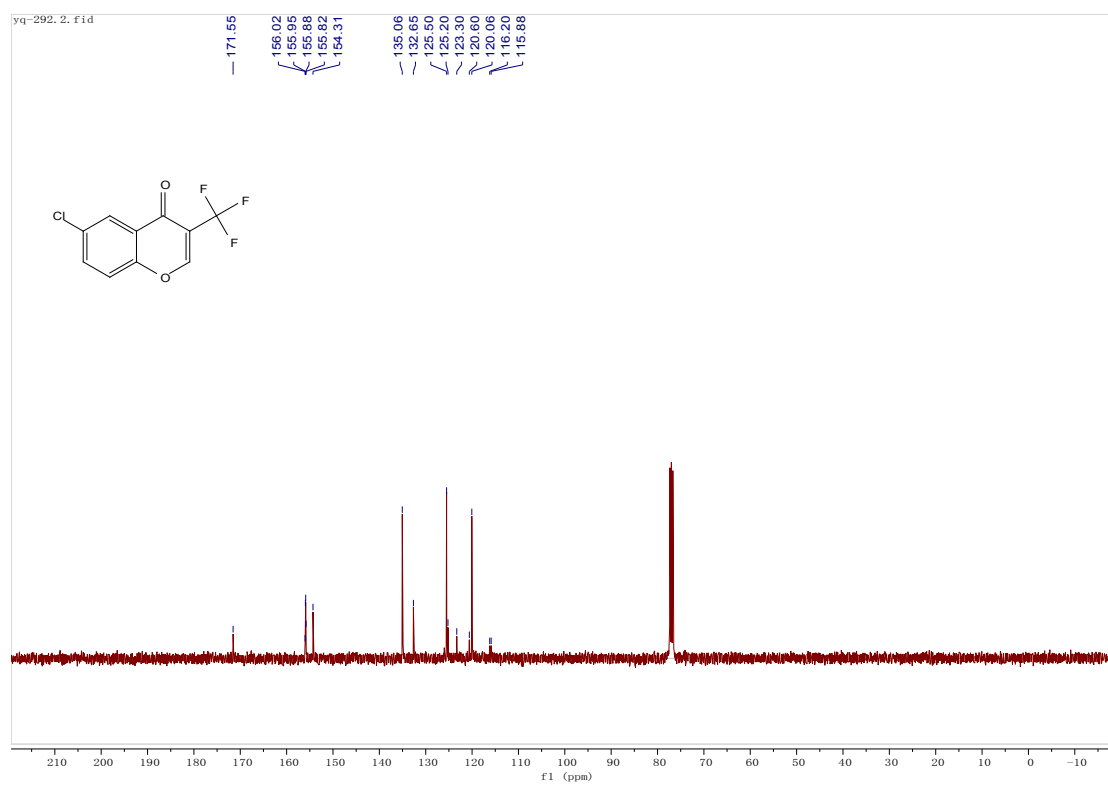
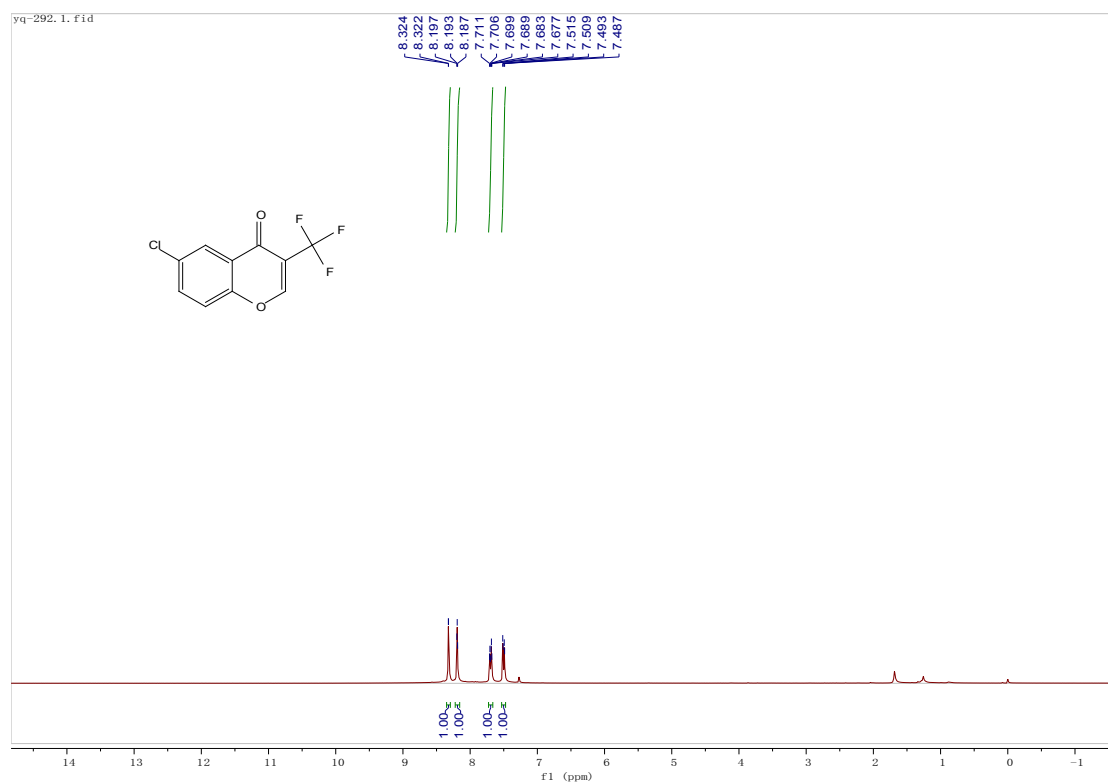


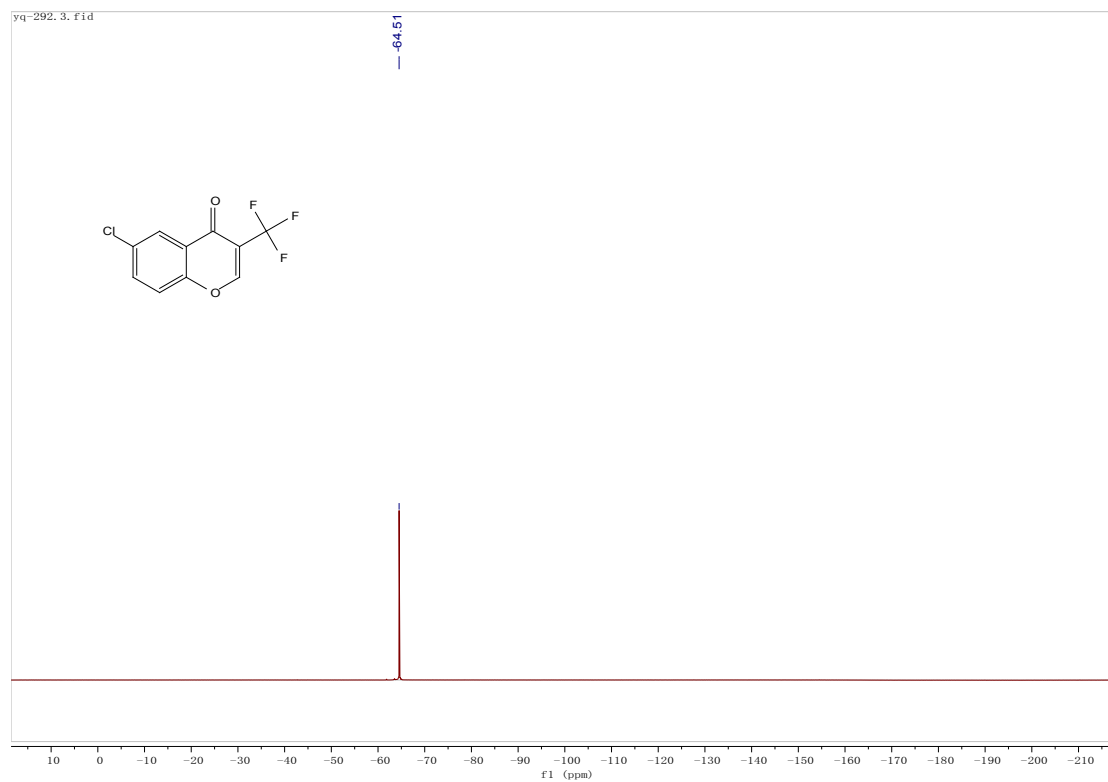
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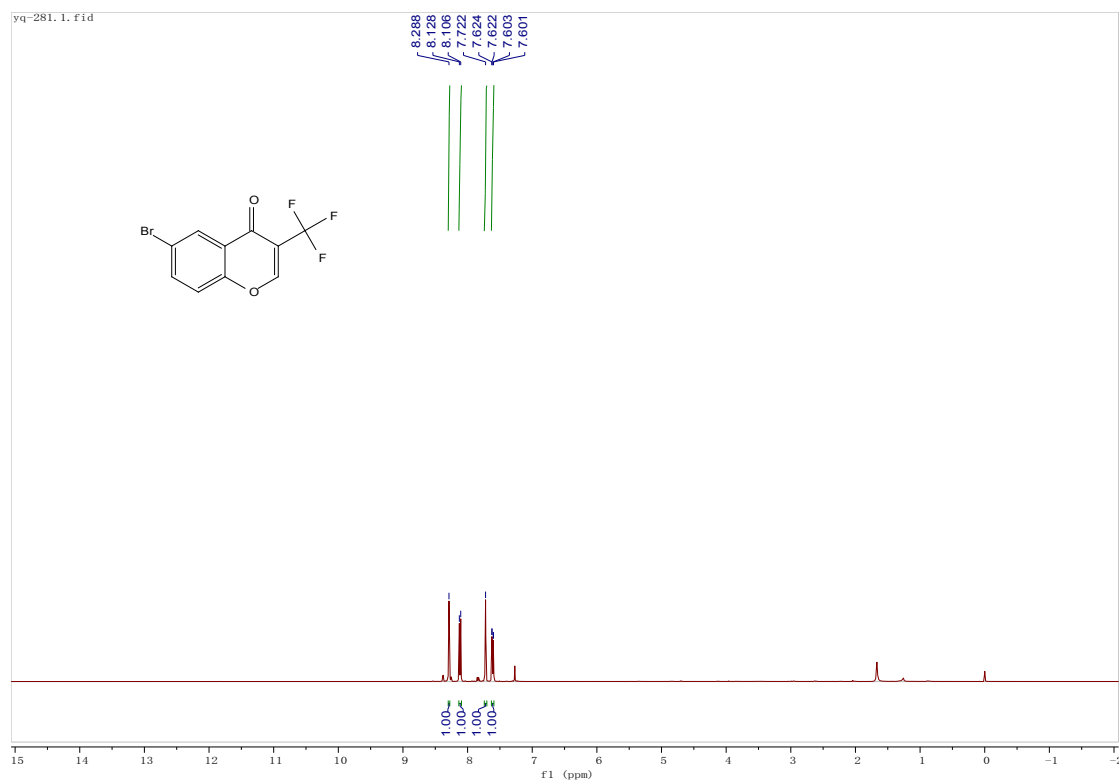
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S20

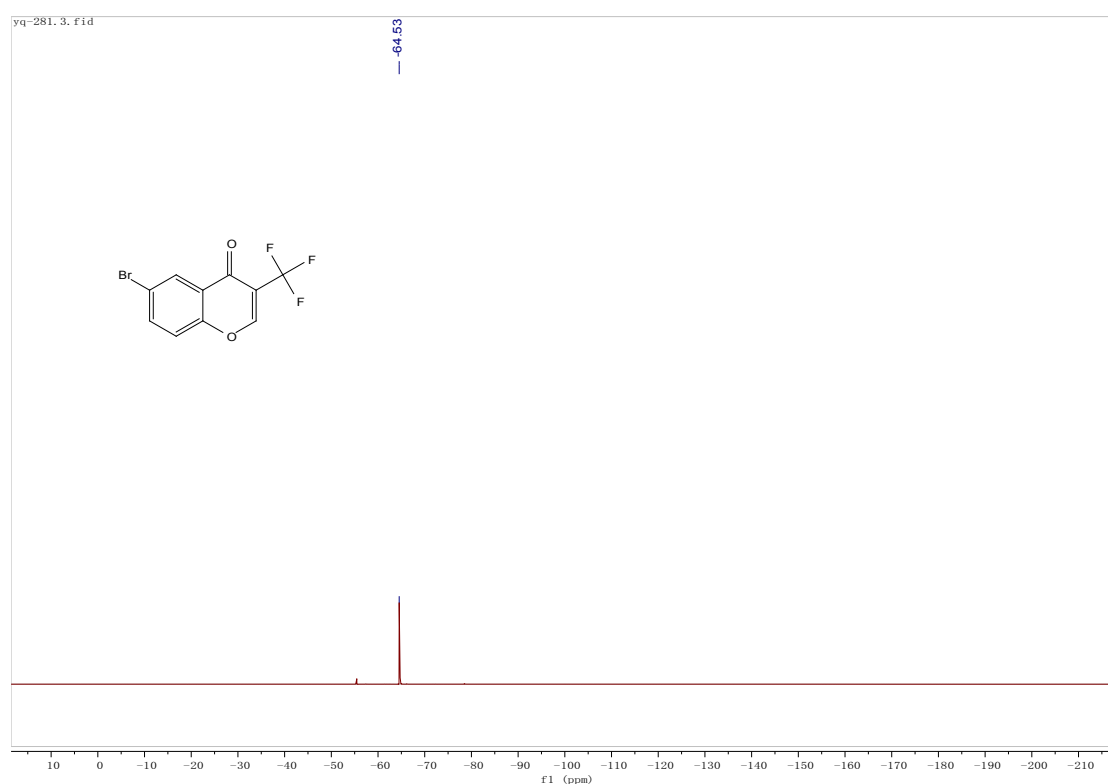
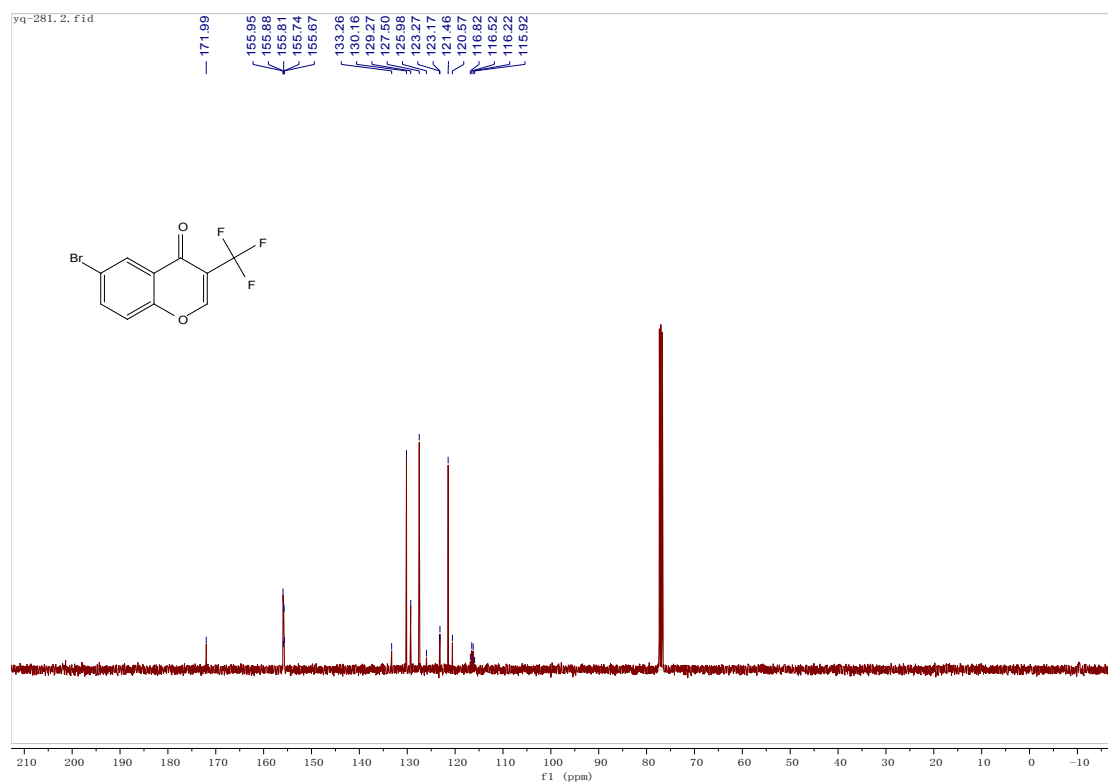




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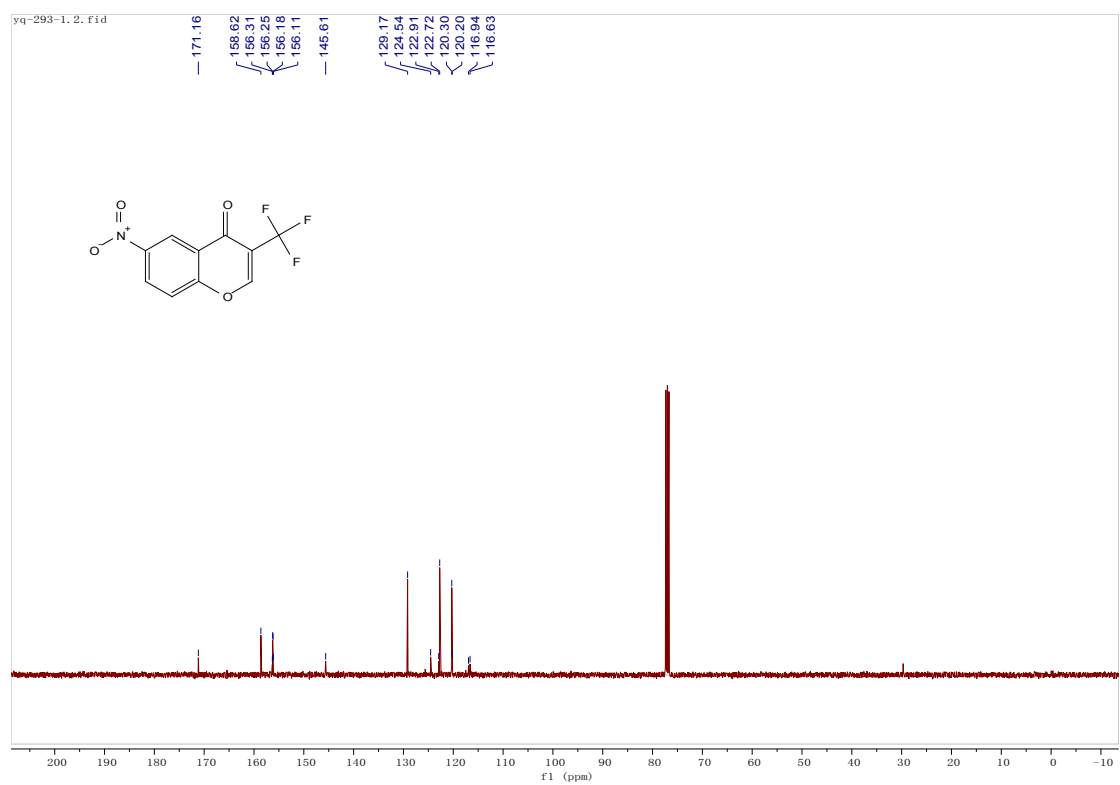
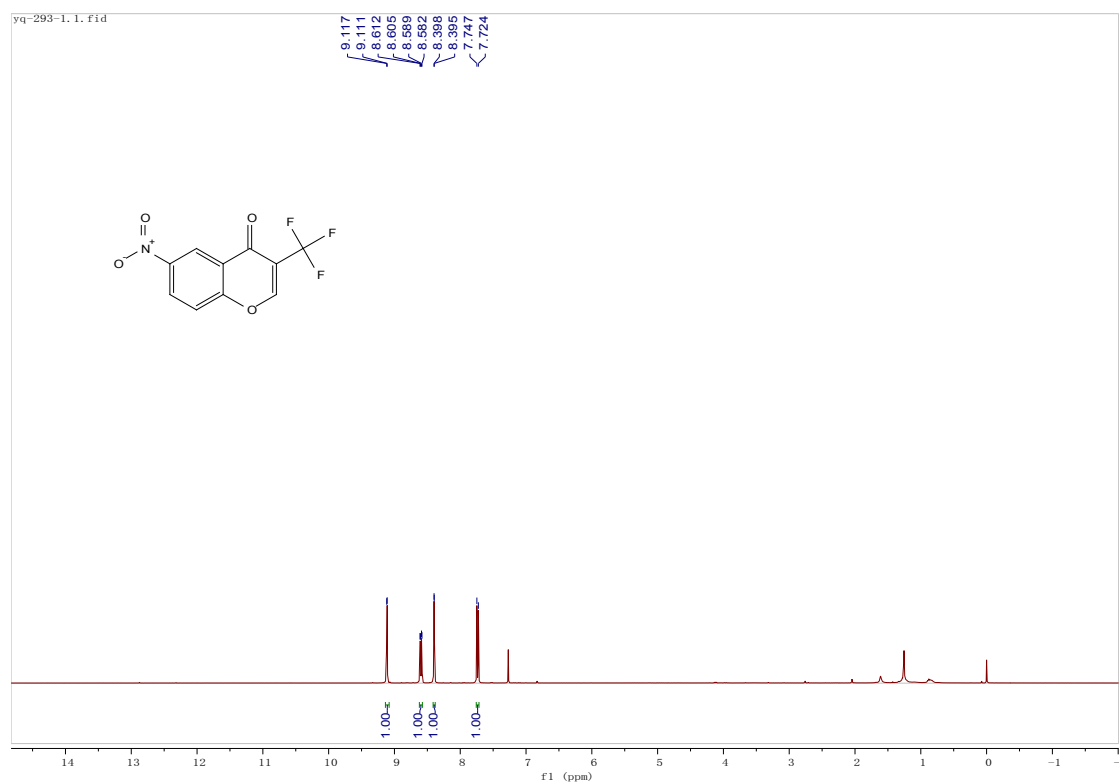


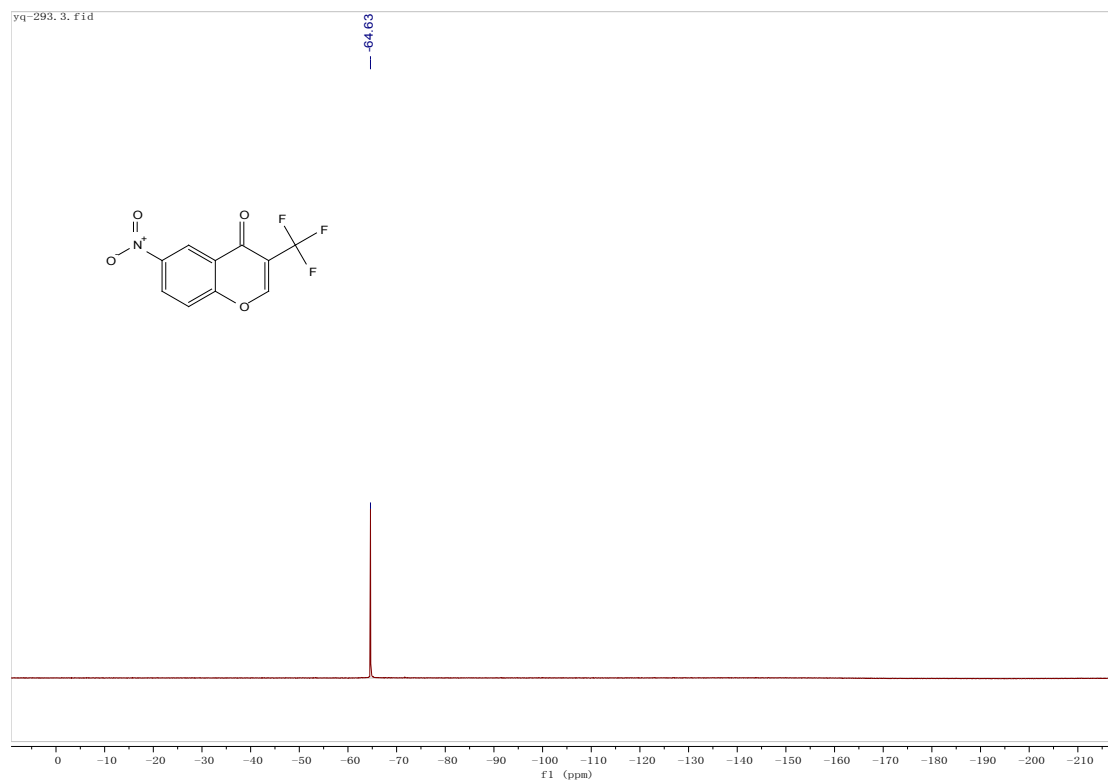
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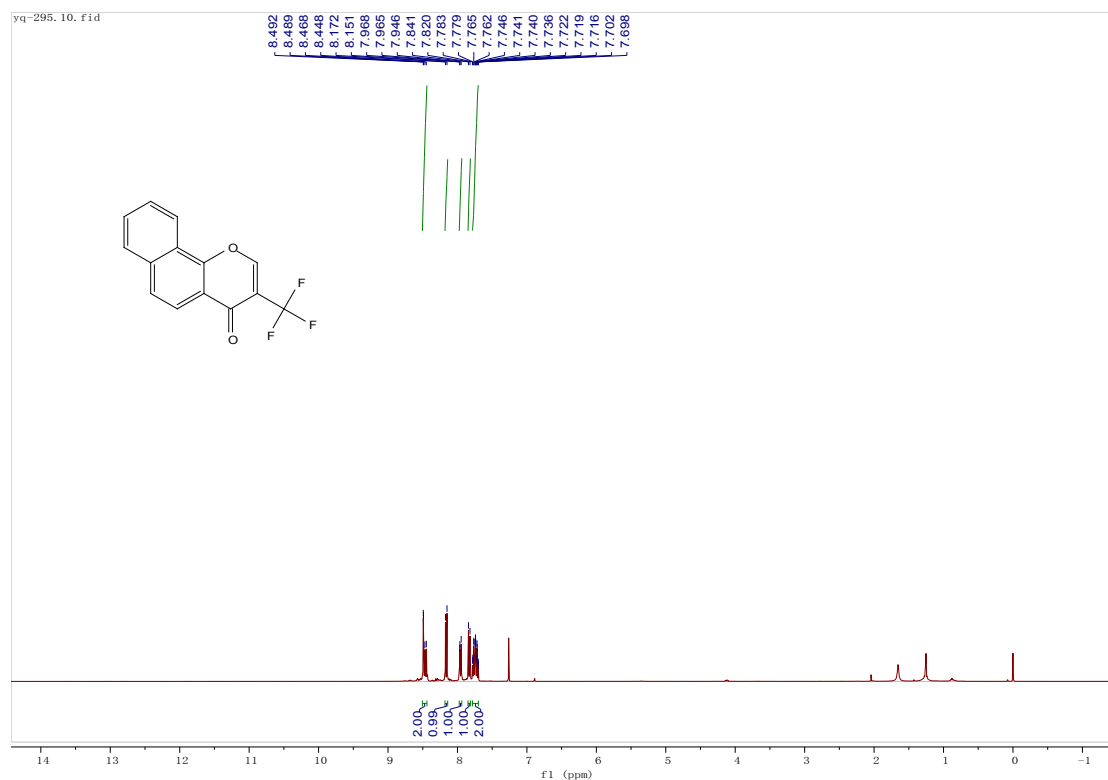
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S23

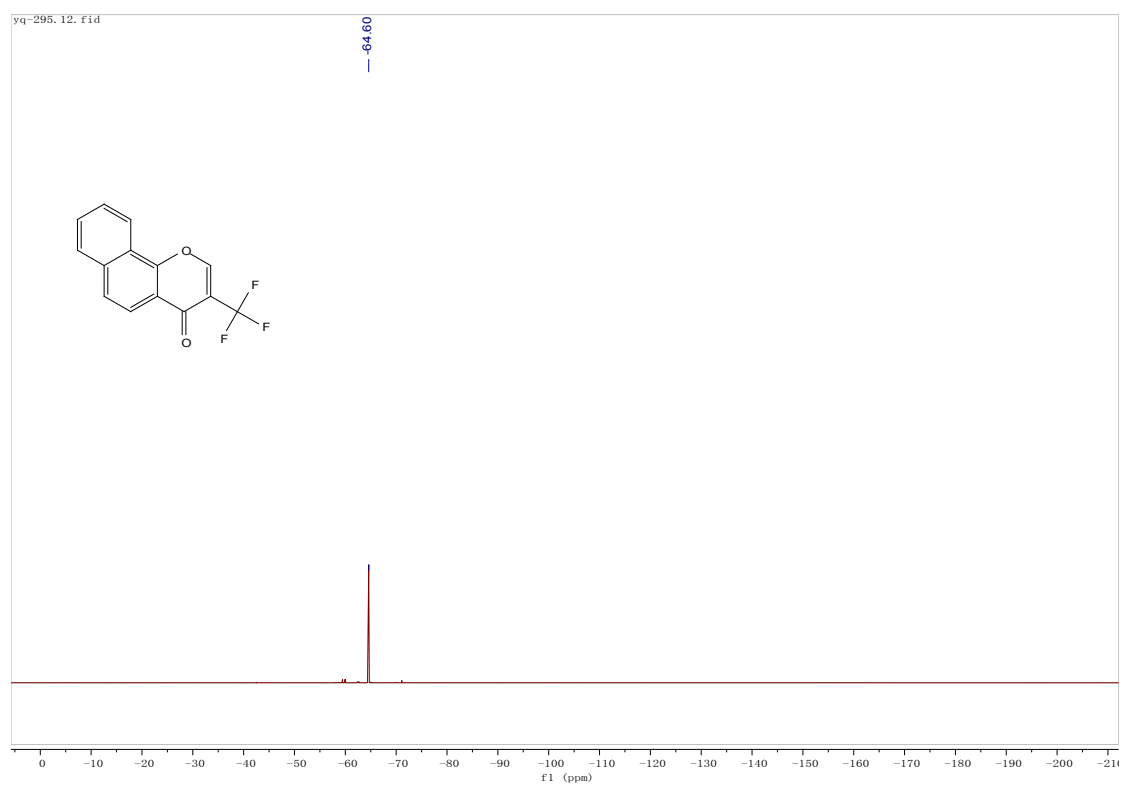
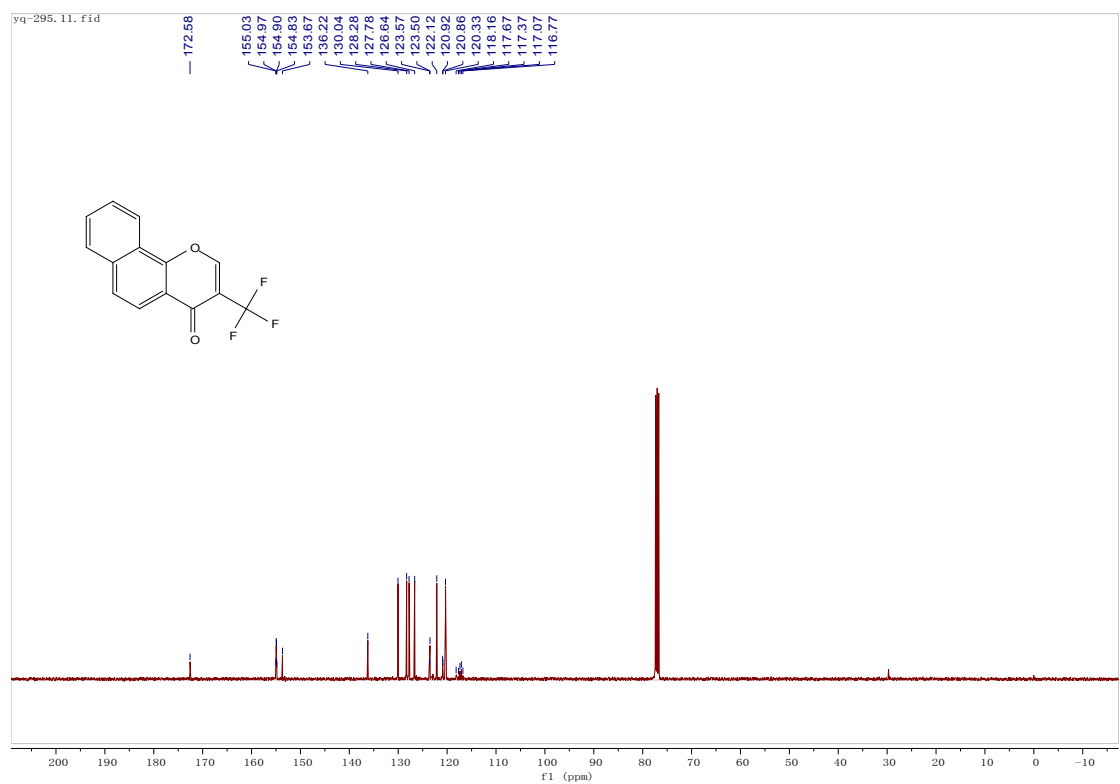




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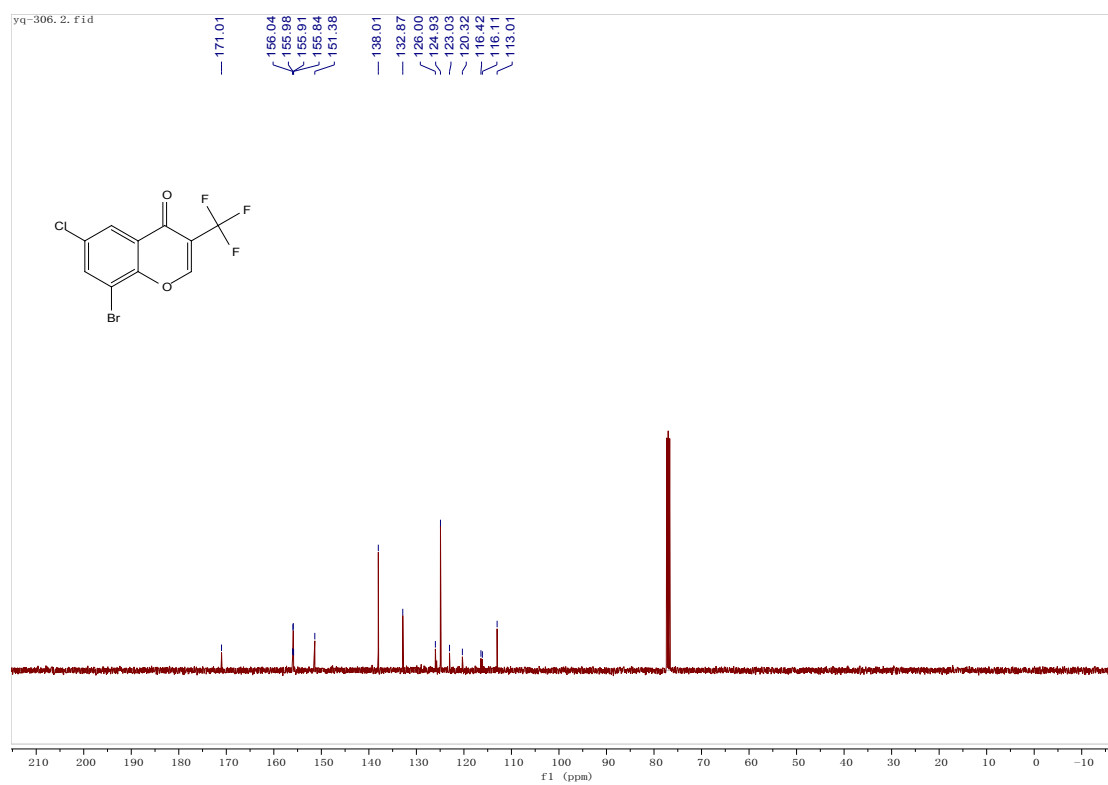
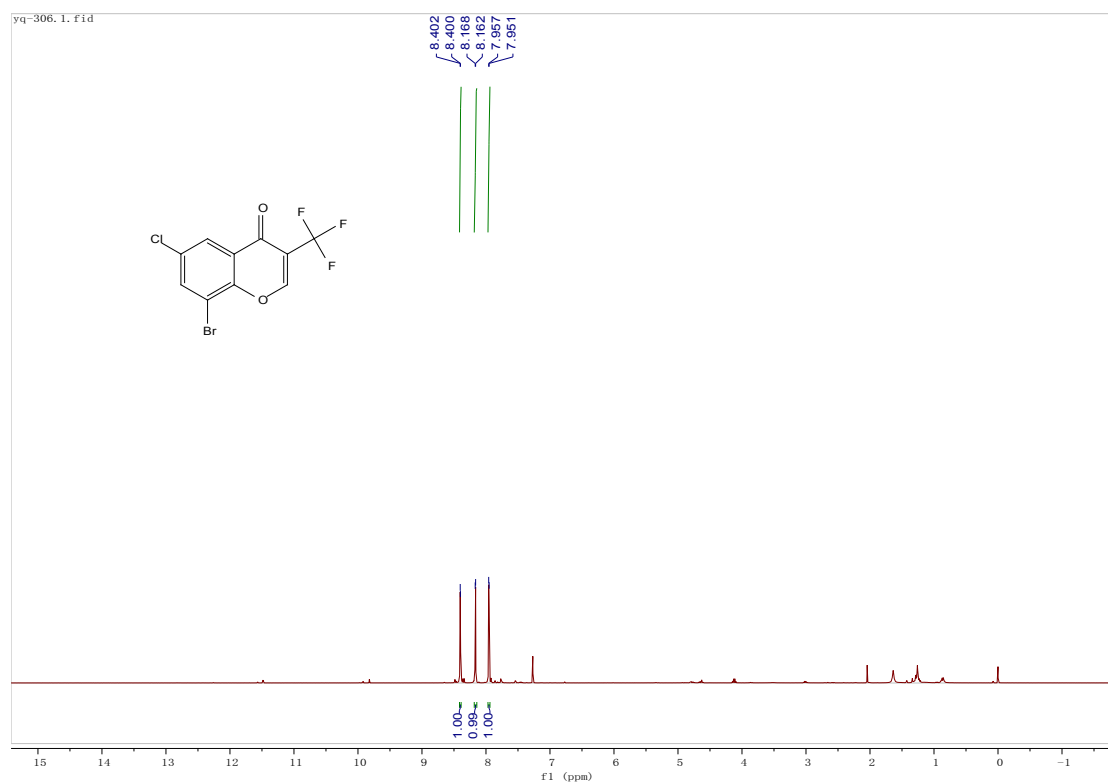


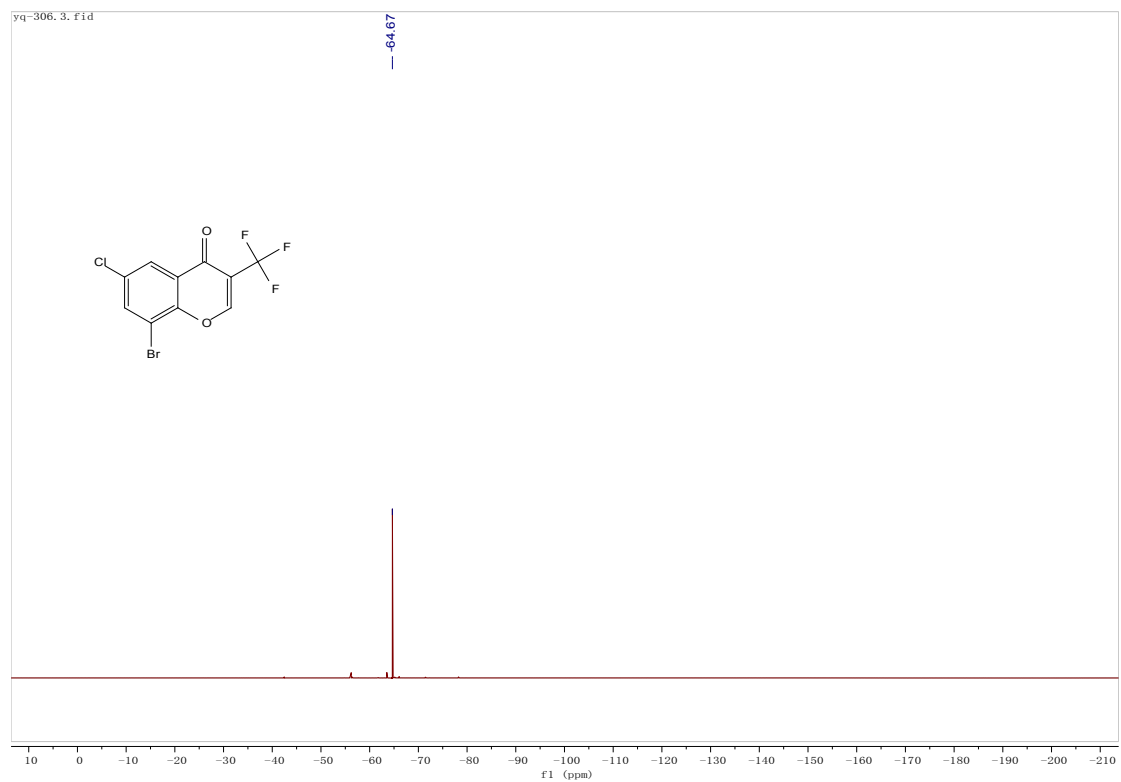
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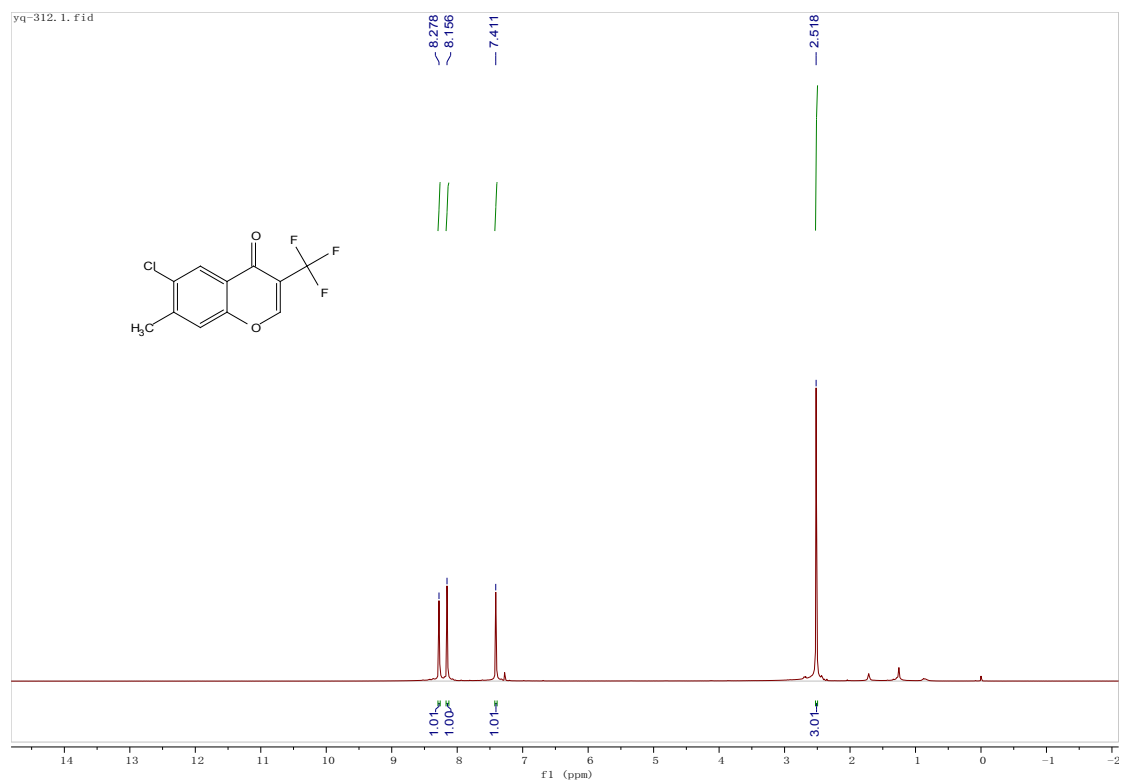
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S26

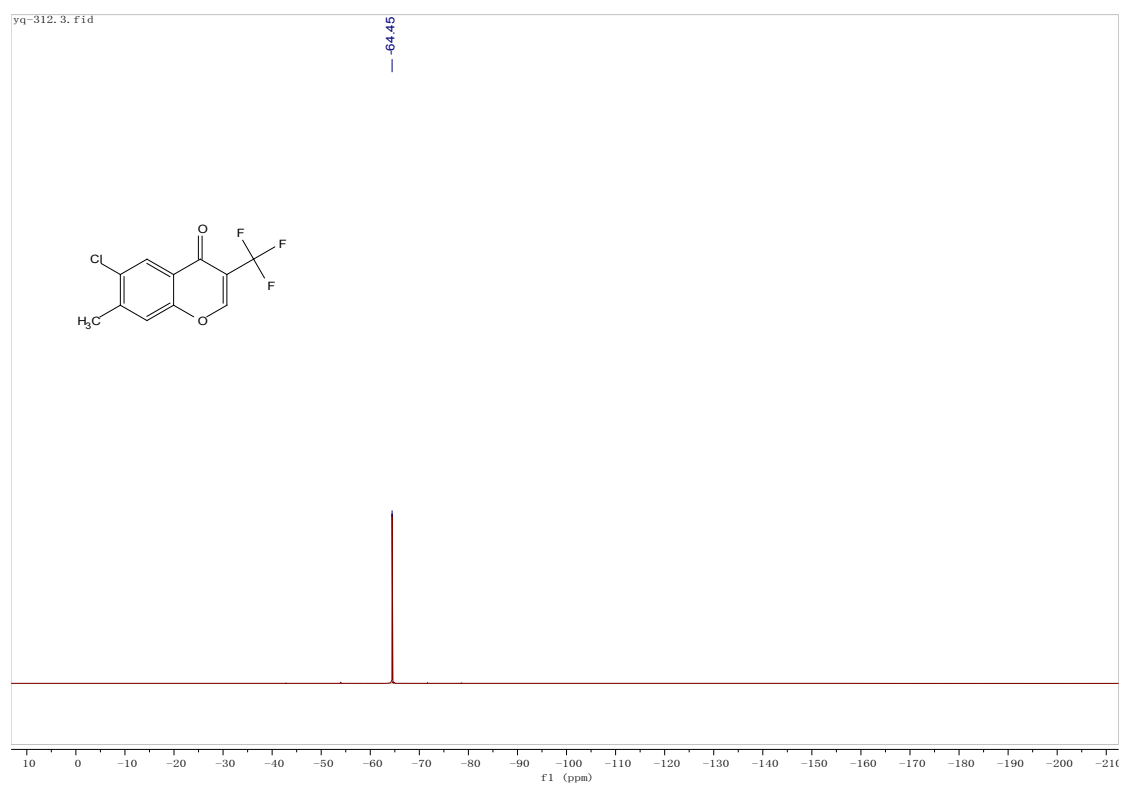
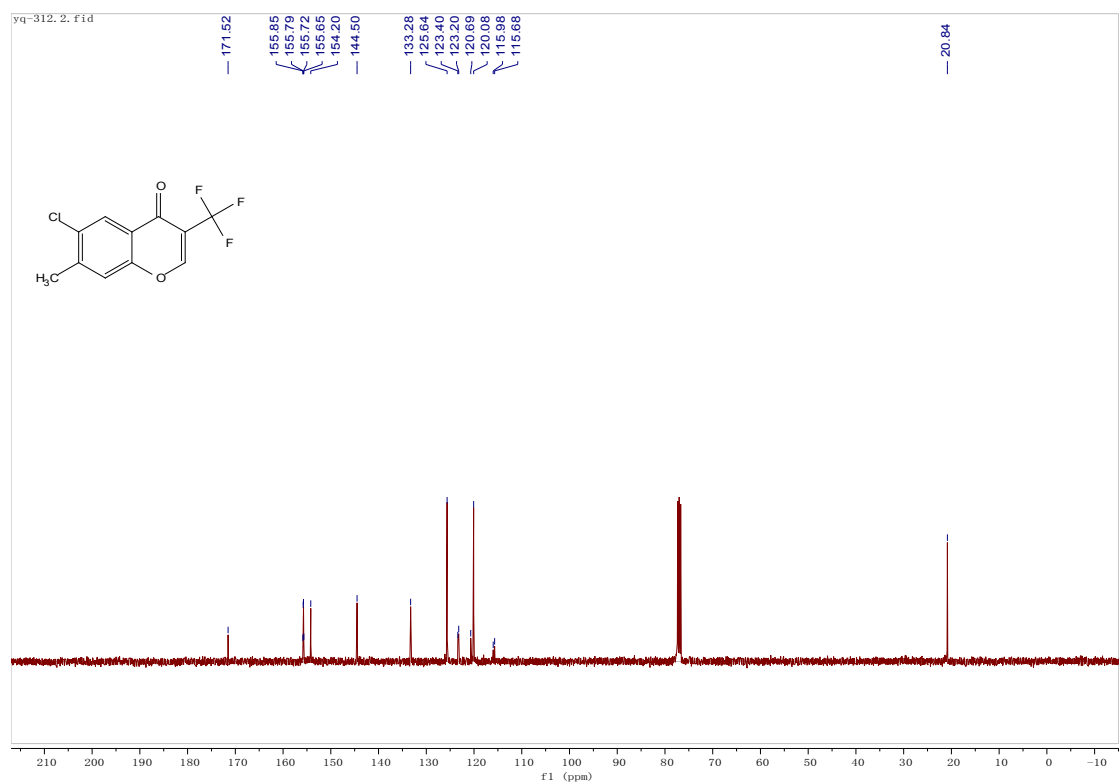




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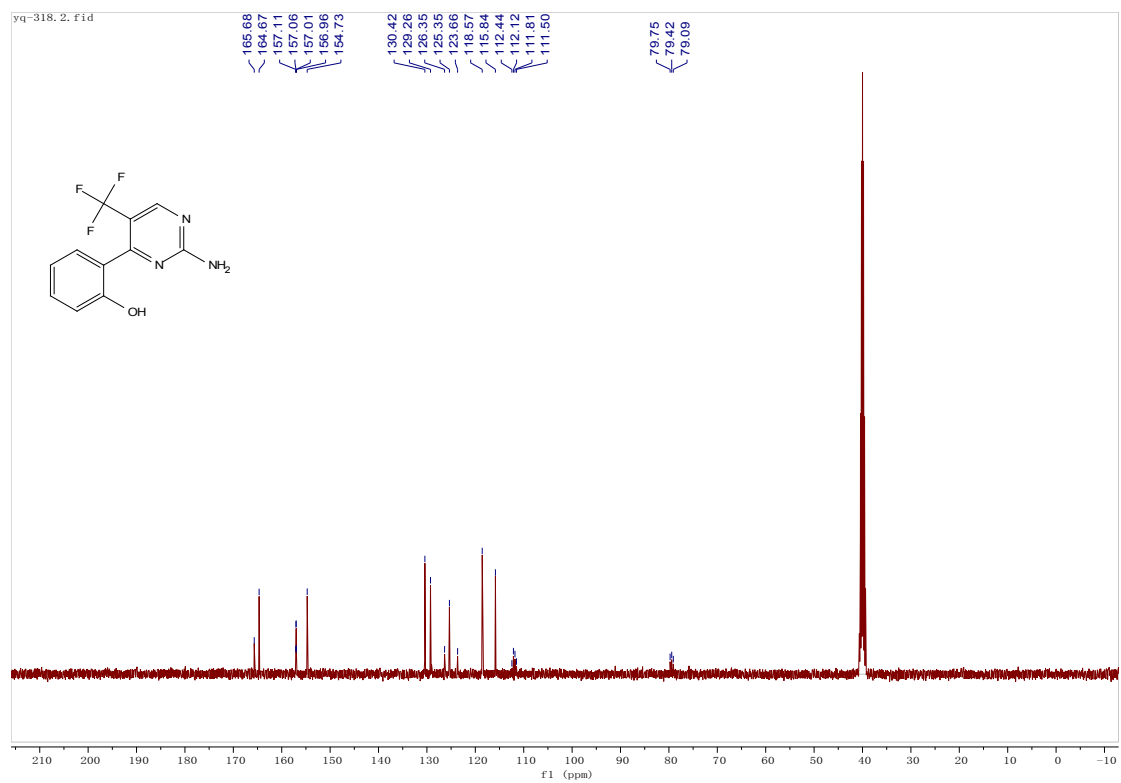
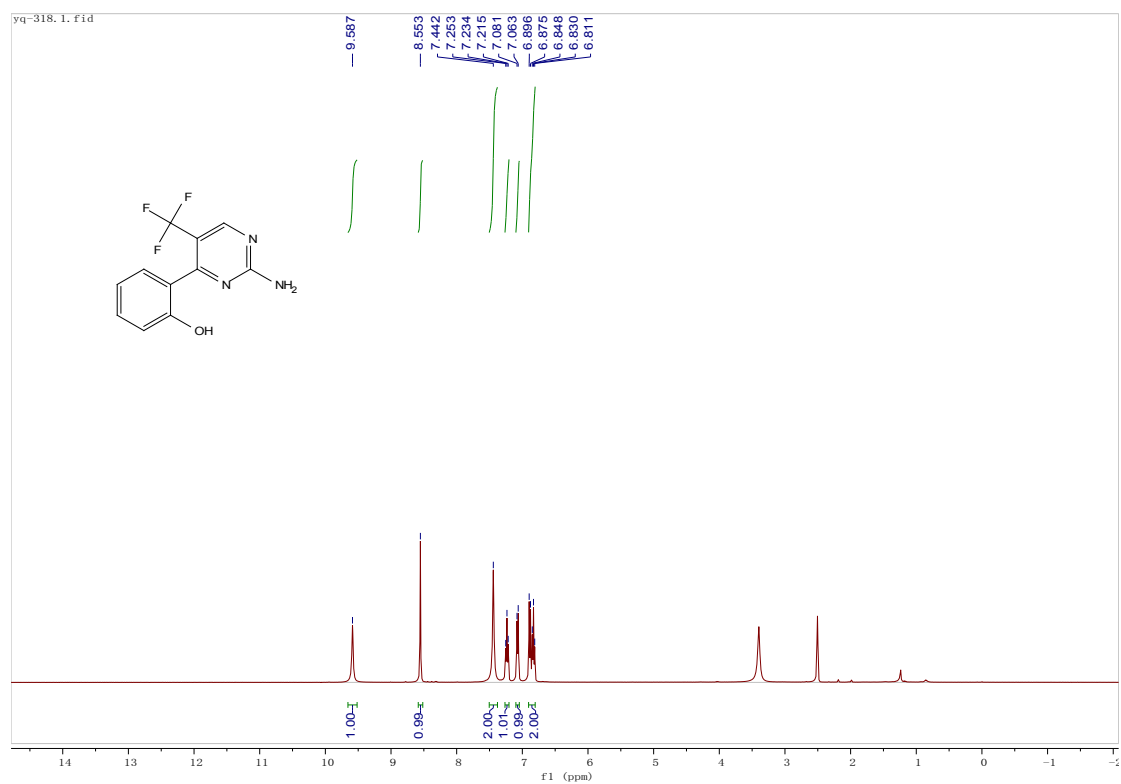


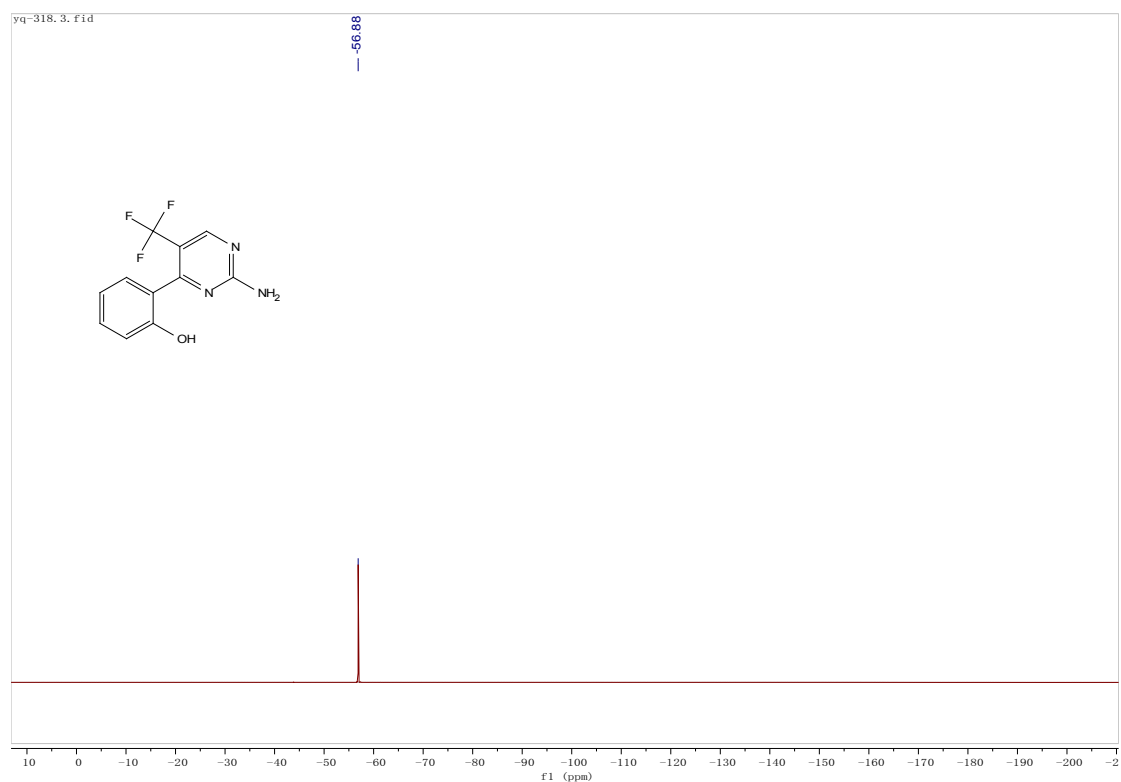
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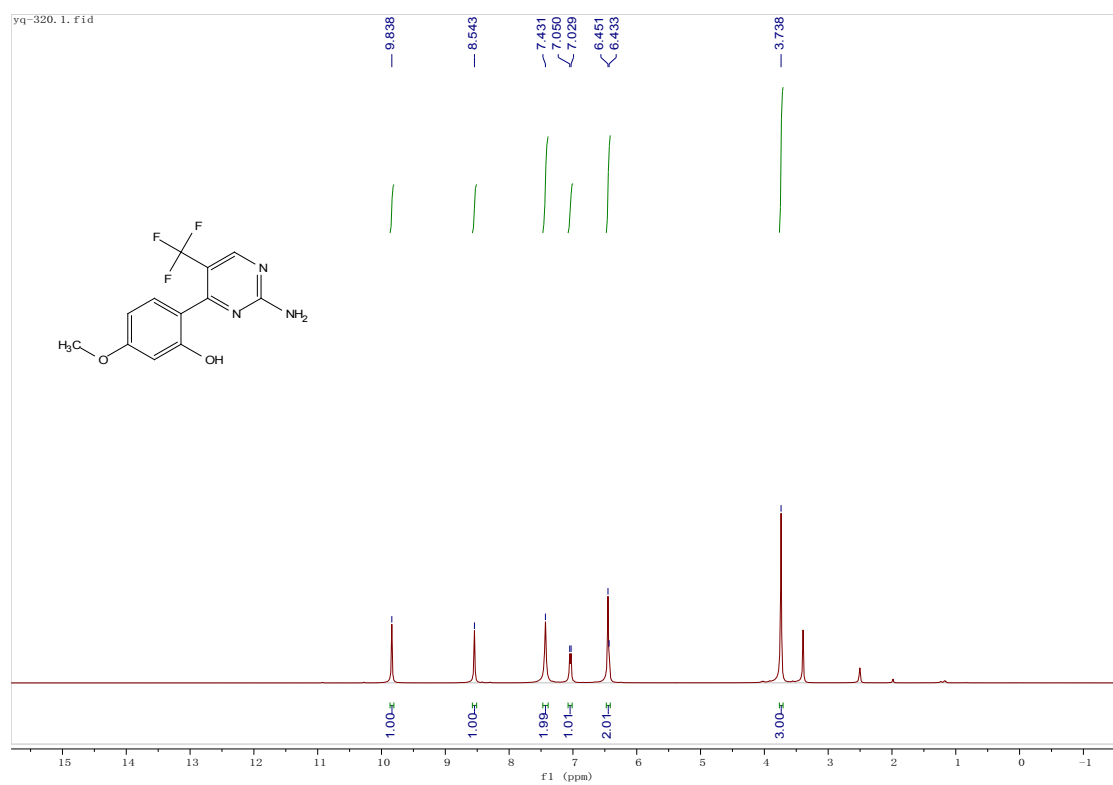
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S29

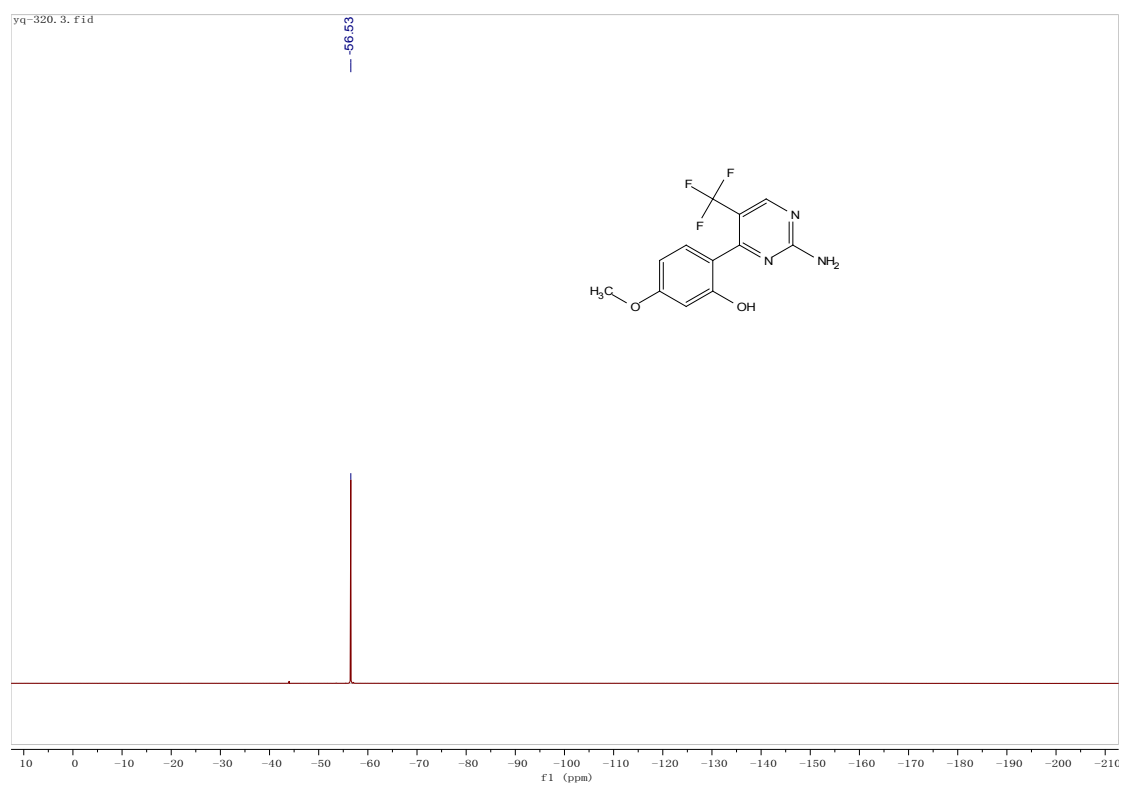
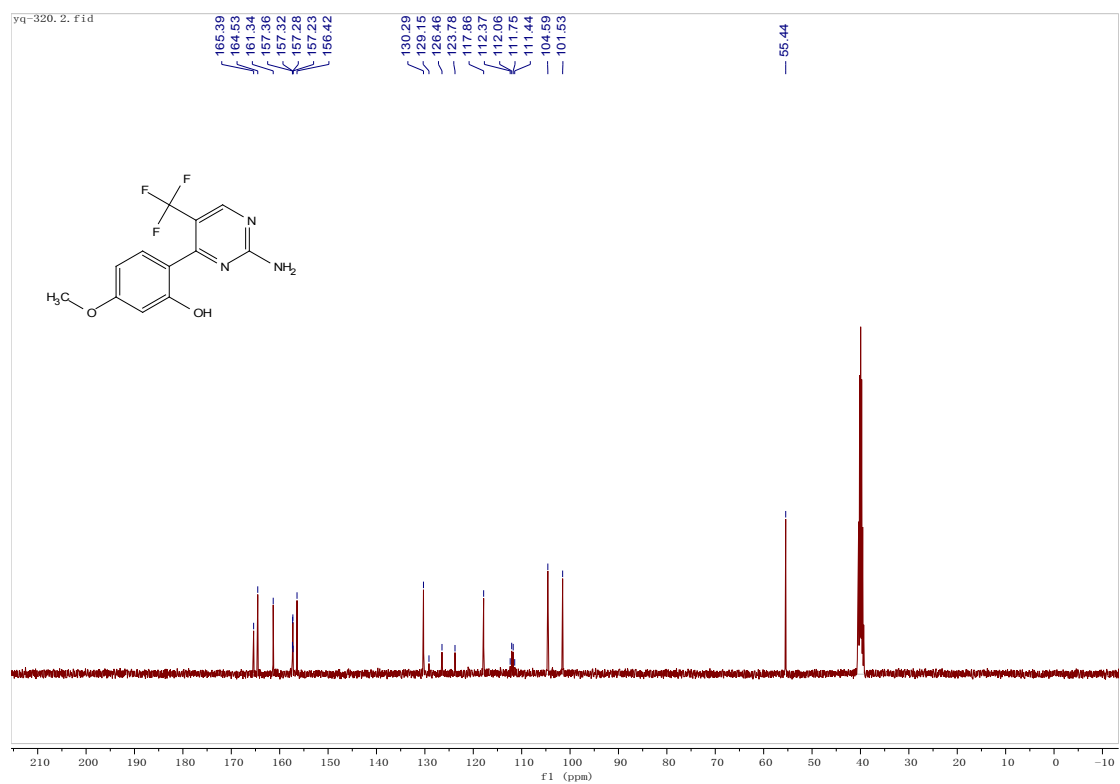




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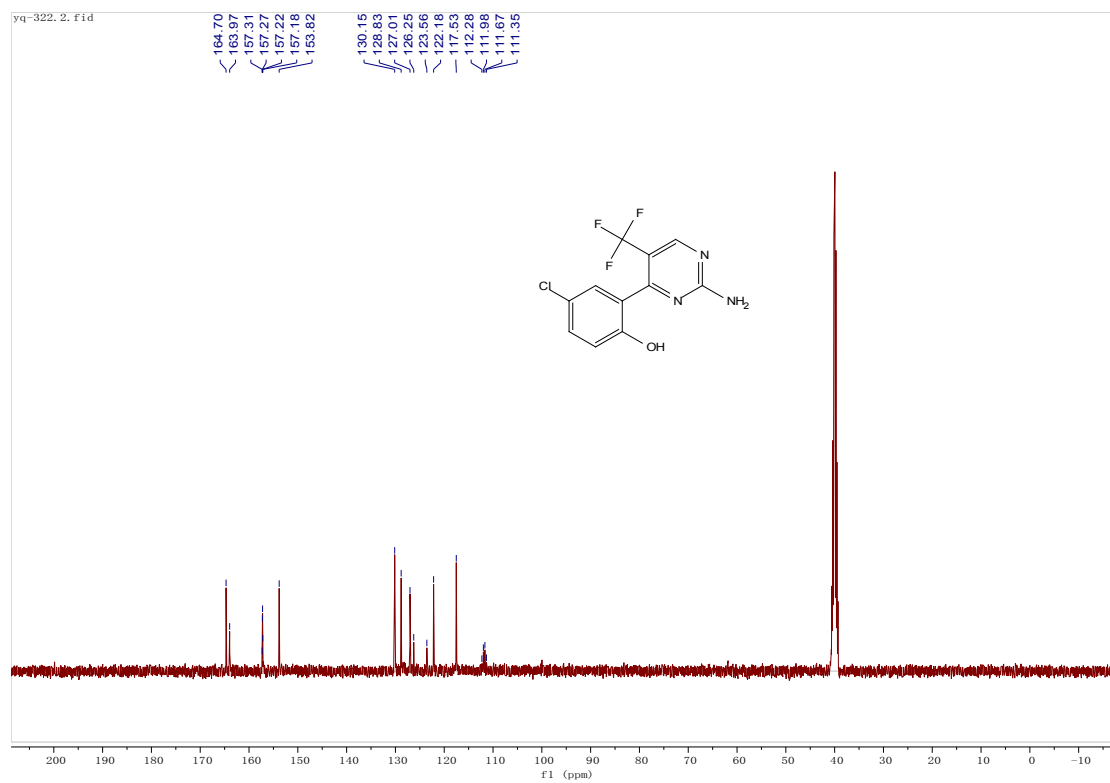
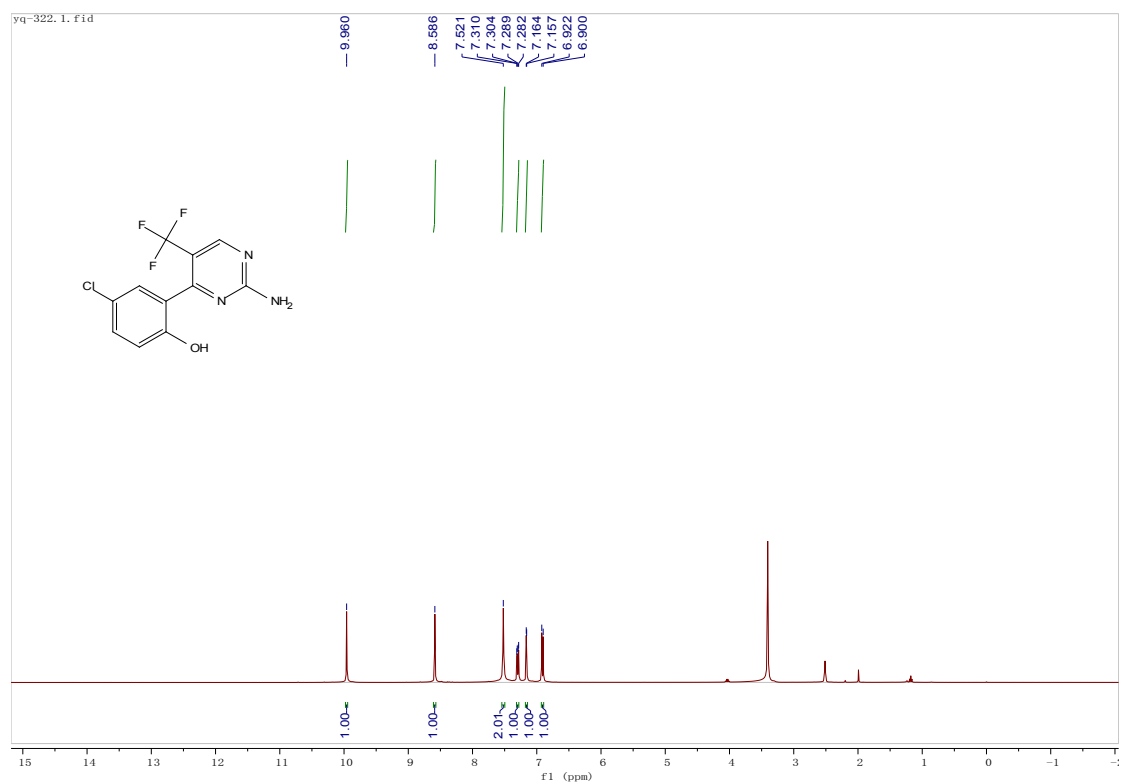


S31



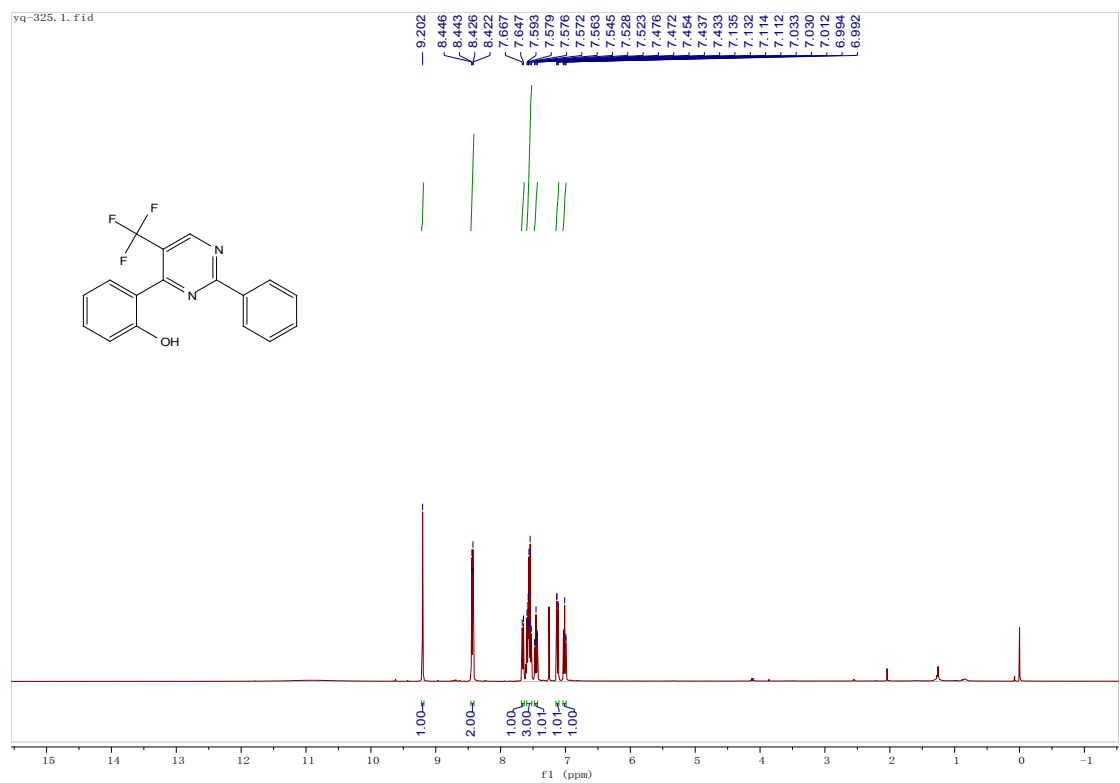
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S32

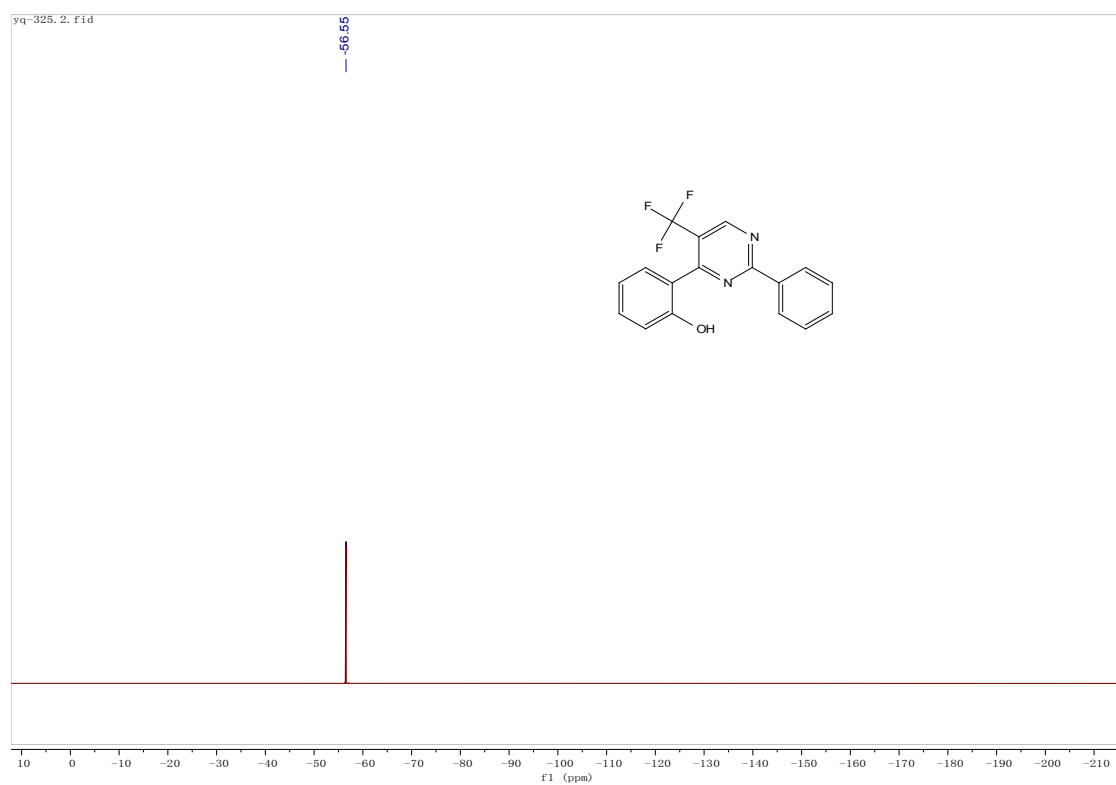
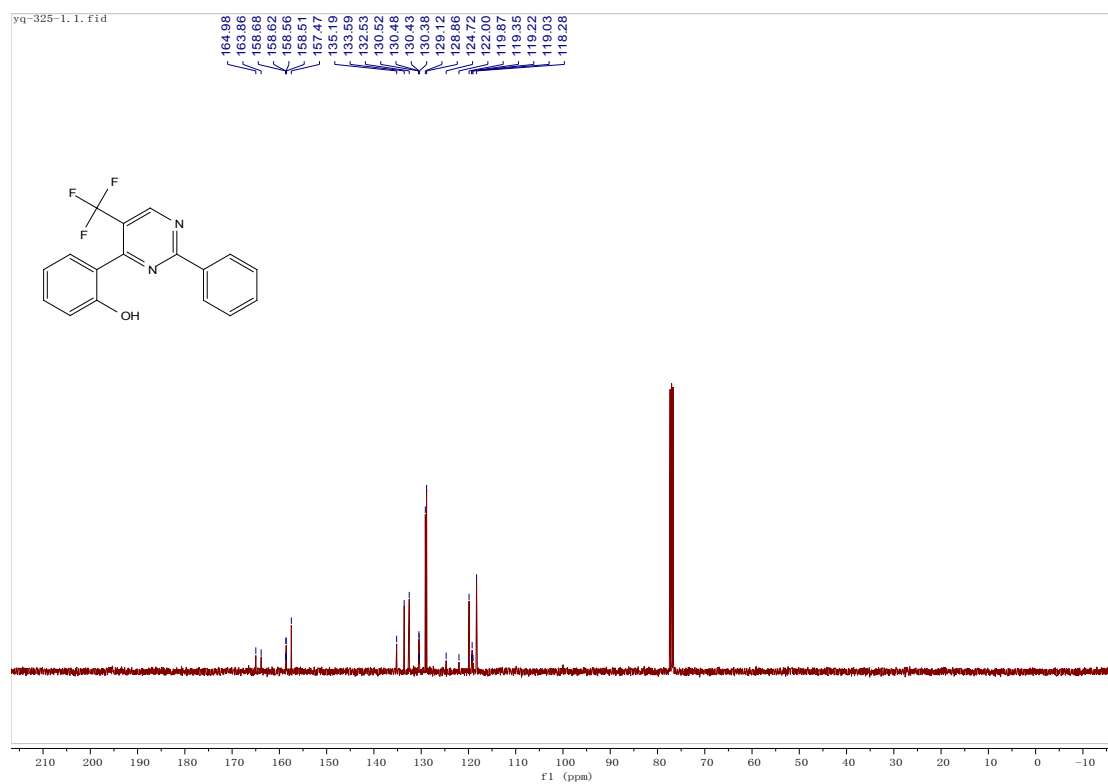




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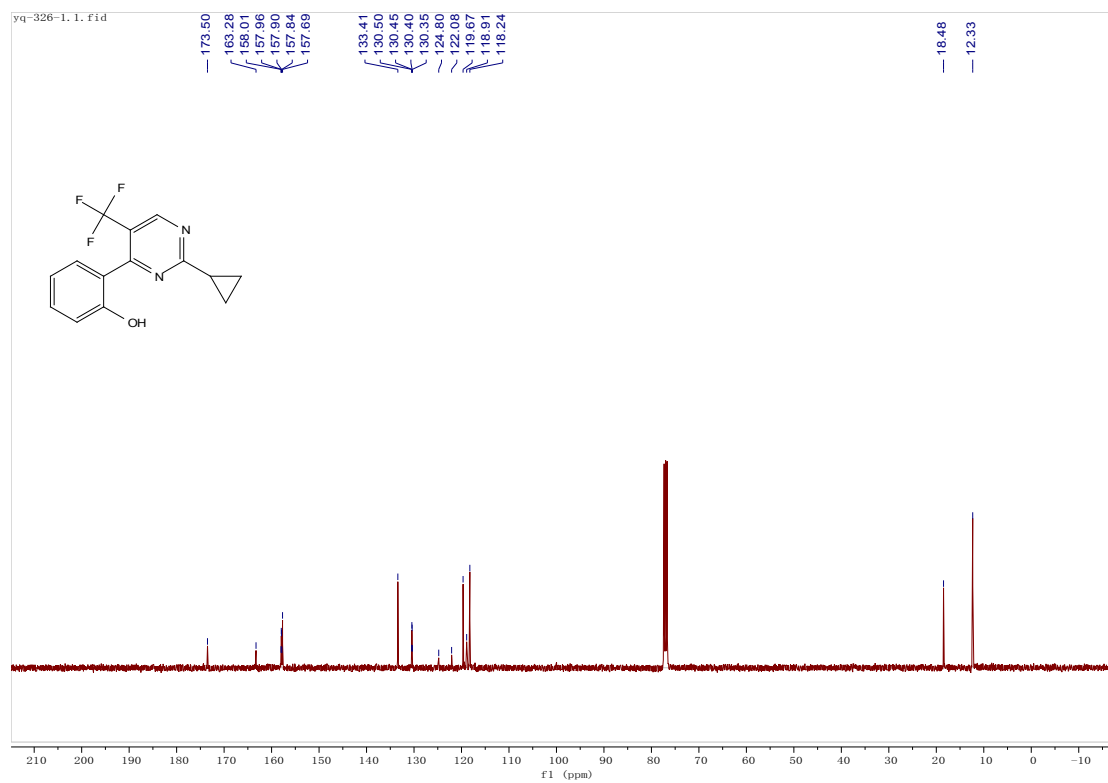
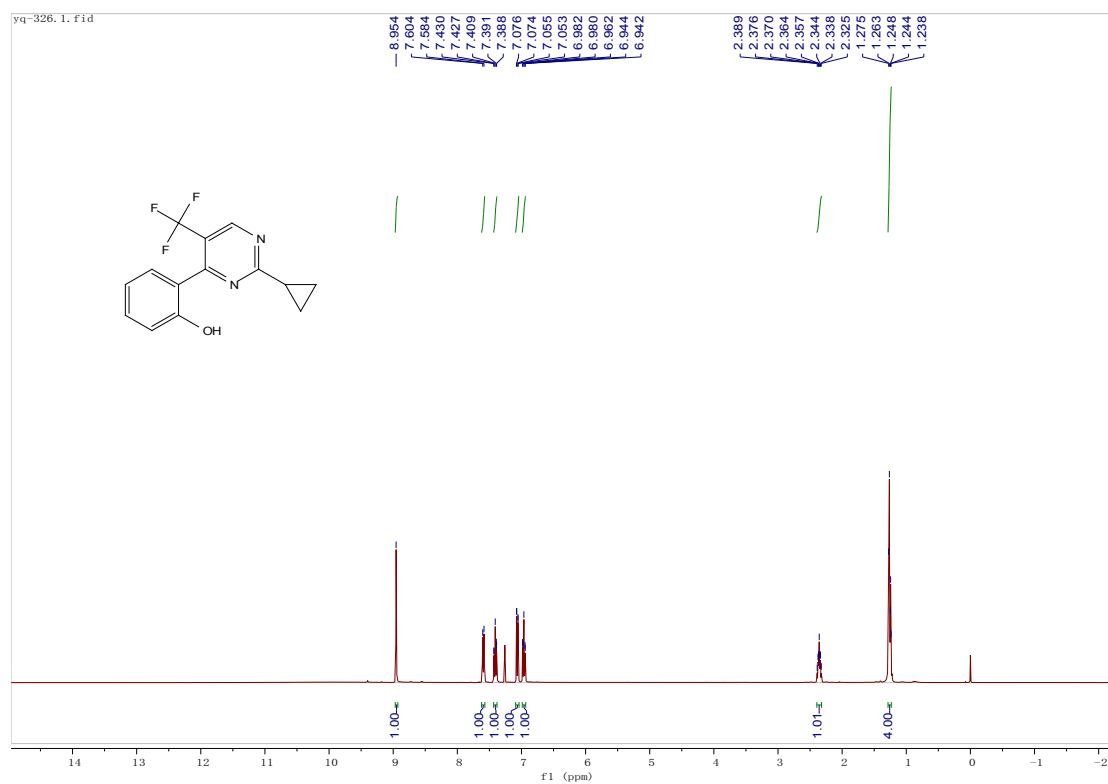


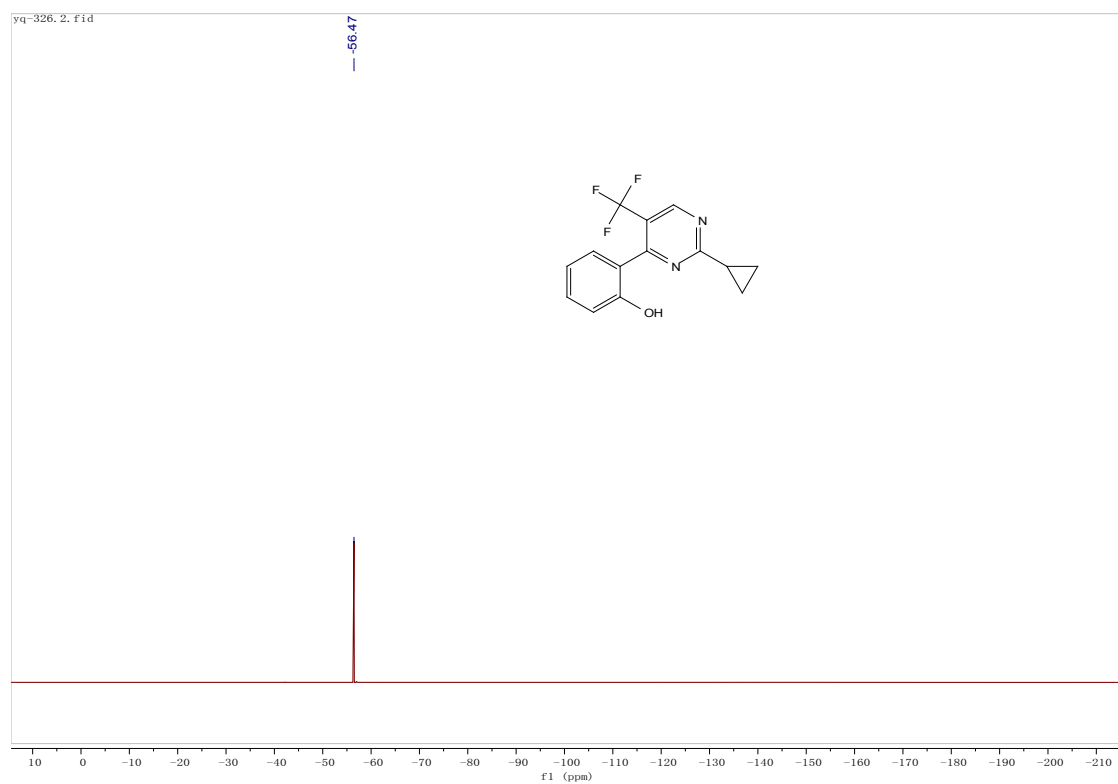
S34



5d

S35





5e